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APPLICATIONS OF BICYCLIC AND CAGE COMPOUNDS

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Final Report

By

Ronald D. Clark

and

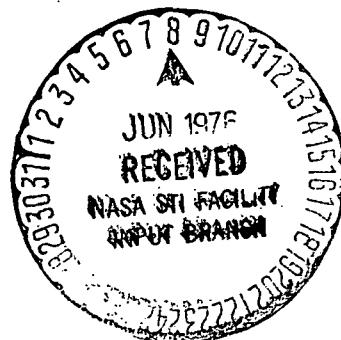
Bennie S. Archuleta

May 30, 1976

New Mexico Highlands University

Las Vegas, New Mexico 87701

Grant Number NSG-804



ACKNOWLEDGEMENTS

The authors wish to acknowledge the excellent secretarial work of Mrs. Ginger Drissel. Without her help, this report could not have been completed. The key punch work of Mrs. Janet Archuleta is also gratefully acknowledged, as is the assistance of Mr. David Rael for computer programming.

Chapters six and seven of this report were taken from the Master of Science Thesis of Bennie S. Archuleta, New Mexico Highlands University, 1976.

ABSTRACT

Three-dimensional bicyclic and cage compounds have been used extensively as polymers, polymer additives, medicinals, and pesticides. Lesser applications have included fuels, fuel additives, lubricants, lubricant additives, and perfumes. Several areas where further work might be useful have been outlined. These are primarily in the areas of polymers, polymer additives, medicinals, and synthetic lubricants.

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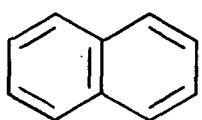
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Chapter 1 - Introduction

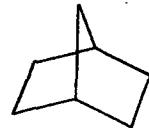
Bicyclic compounds are compounds containing two rings fused together. They may be made in any size beginning with four atoms in the ring. Since carbon is the only element that is known to extensively bond with itself, most bicyclic compounds are organic. Some specific examples of bicyclic compounds that have been made are shown in figure 1-1.



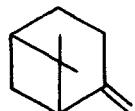
napthalene



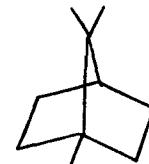
bicyclobutane



norbornane



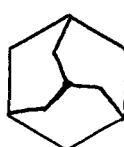
β -pinene



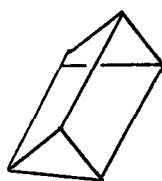
camphor

Figure 1-1. Some known bicyclic compounds.

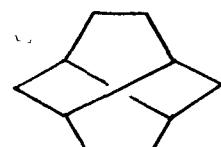
Cage compounds are similar to bicyclic compounds except that they are generally larger and have more rings fused together. The three dimensional shape of cage compounds generally resemble that of a cage. Some specific examples of known cage compounds are shown in figure 1-2.



adamantane



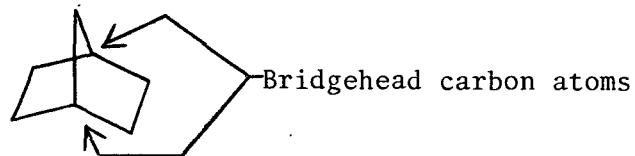
prismane



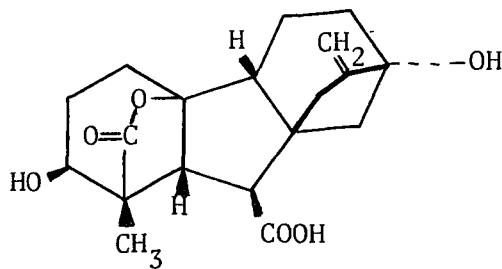
twistane

Figure 1-2. Some known cage compounds.

The atoms where the rings are fused together are known as the bridgehead atoms (e.g. bridgehead carbon atoms for most rings) for both bicyclic and cage compounds.



Bicyclic and cage compounds are very common. Many natural products contain bicyclic or cage systems. For example, gibberellin is a naturally occurring plant growth regulator that has been extensively studied. Many



Gibberellin

of the terpenes and alkaloids found in natural products have similar types of structures.

Studies of the chemical reactivity of these molecules suggest that in general, most large bicyclic and cage compounds are similar to non bicyclic compounds. Smaller systems, however, tend to exhibit special behavior. Compounds containing very small ring systems tend to be highly reactive because of the ring strain. Bicycloheptanes and bicyclooctanes containing functional groups at the bridgehead, however, have been found to be unusually stable. The unusual stability of these materials is so striking that there should be many practical applications for them.

Definitions of the Problem

The present report represents the results of a literature survey of the field of bicyclic and cage compounds. The objective of the project was to identify those types of compounds that have unusual physical and chemical stability, and to determine what practical applications have been found for these types of compounds.

Limitations of the Report

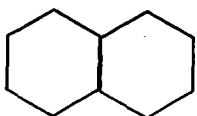
The scope of the project, as outlined above, is tremendous. There have been literally thousands of papers written on bicyclic and cage compounds. For this reason, it has been necessary to limit the scope of the project to more specific areas. We have attempted to make the limitations in such a manner that no significant areas were eliminated, but at the same time, the bulk of the unnecessary material would not have to be included. The specific limitations placed on the project were:

1. Natural products were generally not considered.
2. Only three dimensional molecules (as opposed to planar systems) were considered.
3. Highly olefinic systems were generally not considered.
4. Only articles pertaining to existing or potential applications were included.

Natural products were eliminated because they really constitute a separate field in themselves, and there have been many books and review articles written on all areas of natural products. A few special cases have been included when the compounds seemed to be particularly appropriate, however.

Bicyclic compounds in which the bridgehead carbon atoms are bonded to each other are not considered here. These compounds, while often

exhibiting unique properties of their own, do not usually exhibit the unusual stability associated with the molecules considered in this report. These systems are most easily identified by their name as bicyclo [x.y.0] systems. Examples are shown in figure 1-3.



bicyclo[4.4.0]decane



bicyclo[2.1.0]pentane

Figure 103. Examples of compounds with bridgehead atoms bonded together.

Highly olefinic systems also tend to be more reactive than the types of compounds of general interest here. For this reason, these compounds have also been omitted from the present study.

Since the objective of the project is to determine practical application for bicyclic and cage compounds, one of the most important ways in which the project was restricted was to limit the study to only papers that discussed existing applications, or obvious future applications. For this reason, the chapters discussing theoretical considerations are selective rather than comprehensive in scope.

Approach

The literature search consisted of a search of chemical abstracts. From the first Decennial index through the Eighth Collective Index, the search was conducted by hand. A computer search was provided by the Technical Applications Center at the University of New Mexico, Albuquerque,

New Mexico 87133 for material published between 1972 and June, 1975.

The topics searched were

bicyclo	dioxabicyclo
azabicyclo	thiabicyclo
diazabicyclo	cage
oxabicyclo	adamantane

After the first couple of months work on the hand search, it became obvious that there were so many duplicate listings for the same compound that much time was being wasted looking up the same papers over and over again. As a consequence, productivity was extremely low. As the problem continued to get worse, it became obvious that a solution would be necessary.

The solution finally reached was to have all of the pertinent Chemical Abstract entries punched on computer cards and sorted. A serial number was assigned to each entry so that it could be correlated with the original source if necessary. This procedure brought all of the duplicate entries together and made it possible to only look up the abstract one time. A communication on this procedure was submitted to the Journal of Chemical Education in October, 1975, and is now in press (the expected publication date is fall, 1976).

References

Two types of references are used in this report. These are listed as References and Bibliography. The references are all discussed in the body of the report. When only the abstract of the paper was available, the chemical abstracts reference follows the main reference. When the actual paper was used as the reference, no abstract reference is given. The Bibliography section covers papers that are closely related, but

not discussed in the text. The title of the paper is included in this case as an aid to those interested in material in the Bibliography.

Chapter 2 - Reactivity of Bridgehead Systems

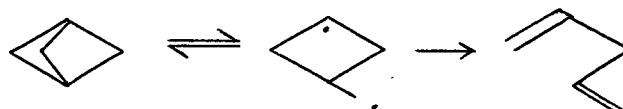
The reactivity of bicyclic systems varies considerably with ring size. The small systems are generally highly reactive. Intermediate sized systems (particularily bicycloheptane and octane) generally tend to be unreactive. Reactivity generally increases again as ring size increases until finally the systems tend to react much like normal compounds.

Bicyclopentanes

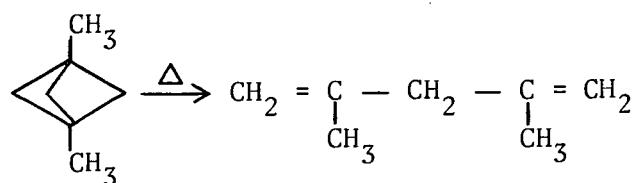
The smallest molecule that qualifies as a three-dimensional bicyclic molecule is bicyclo[1.1.1]pentane.



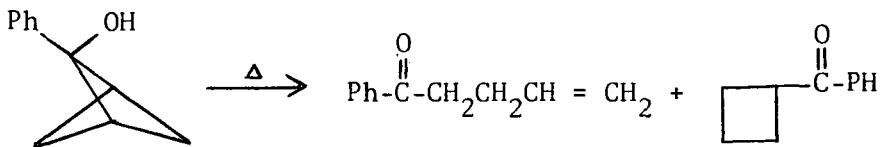
Thermal decomposition of this material was carried out by Srinivasan.¹ The only product isolated between 553.0 and 582.0°K was 1,4-pentadiene. The decomposition was first order and a free radical mechanism was proposed.



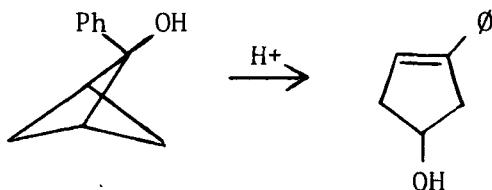
Pyrolysis of 1,3-dimethylbicyclo[1.1.1]pentane gave only 2,4-dimethyl-1,4-pentadiene under similar conditions.



Thermal decomposition of 2-phenylbicyclo[1.1.1]pentane-2-ol gave 1-phenyl-4-penten-1-one (65%) and cyclobutylphenyl ketone (35%) between 135 and 208°C. A mechanism involving a 1,5-H transfer from a diradical



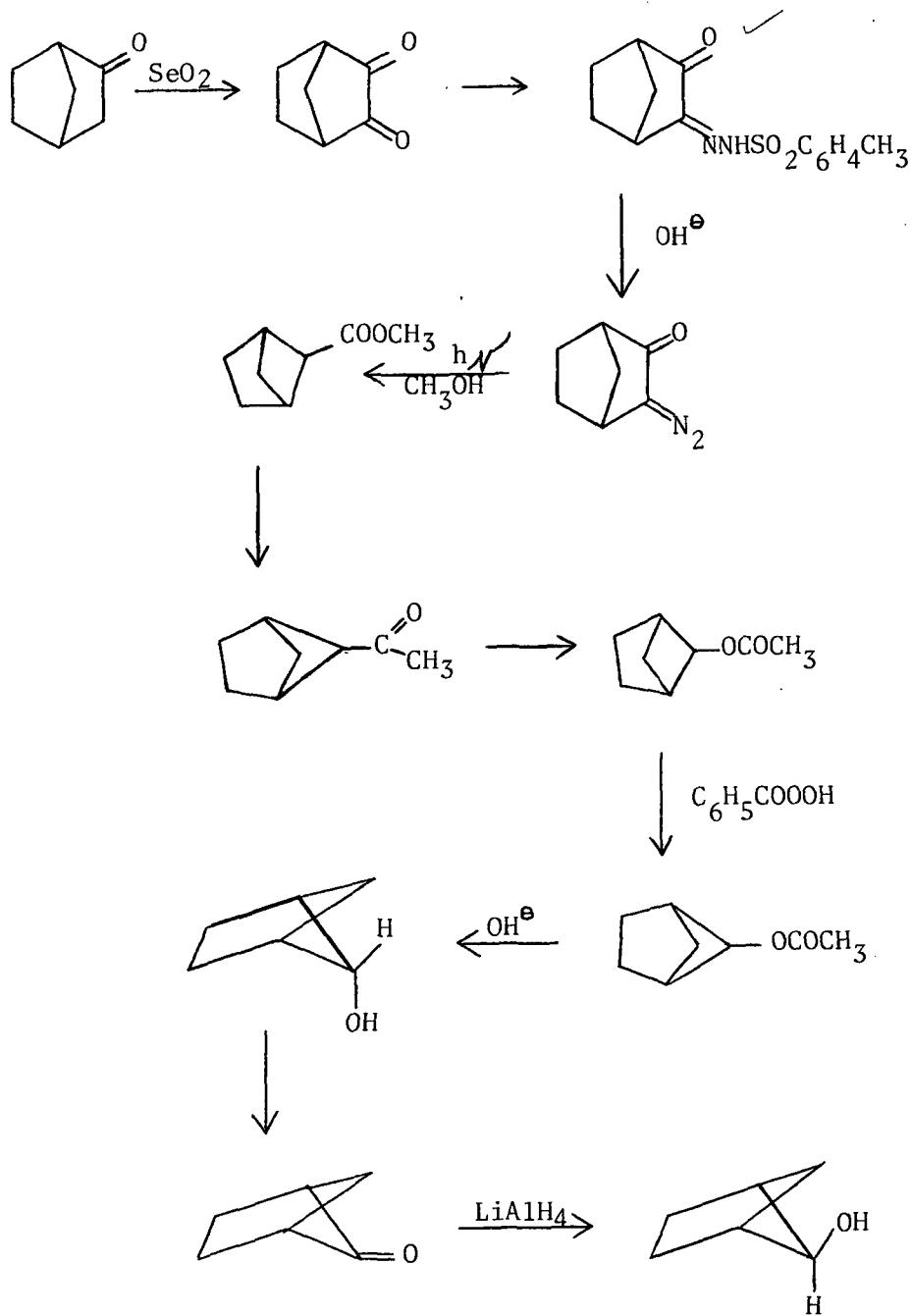
intermediate was proposed.² In acid solution, 2-phenylbicyclo[1.1.1]pentane-2-ol was unstable and rearranged to 3-phenyl-3-cyclopenten-1-ol.



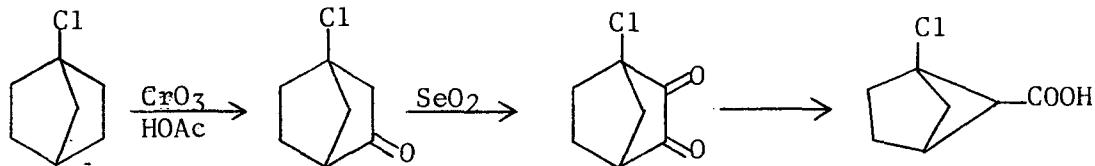
A bicyclo[2.1.0]pentyl cation intermediate was proposed for this reaction.

Bicyclohexanes

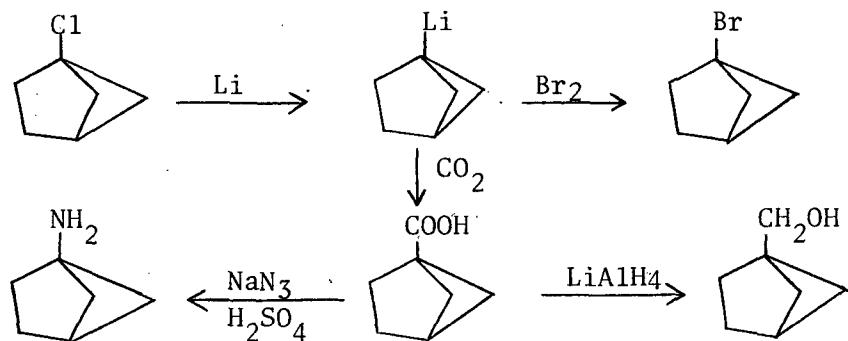
Bicyclohexanes are somewhat less reactive than bicyclopentanes. The only three-dimensional version is bicyclo[2.1.1]hexane. Several routes to the ring system have been devised. In general, these routes have involved ring contraction reactions. For example, Wiberg³ carried out the following sequence of reactions to obtain the ring system.



When a chloro group was located at the bridgehead of the norbornane starting material, it remained in the product.



Once the bridgehead chloro compound was available, other derivatives could be readily made.⁴ For example, Wiberg⁵ also carried out the following reactions.



Another interesting route to bicyclo[2.1.1]hexanes has been reported by Cairncross and Blanchard.⁶ These authors obtained the bicyclohexane ring system via a cycloaddition reaction between 3-methylbicyclo[1.1.0]butanecarbonitrile and an appropriate olefin.



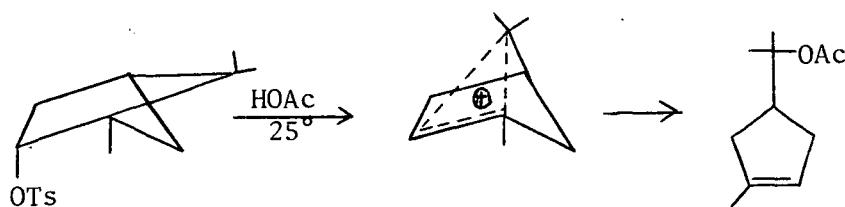
Olefins which were used included butadiene, acrylonitrile, maleonitrile, fumaronitrile, ethylene, styrene, p-methoxystyrene, and 1-(N,N-dimethylamino)cyclopentene. Papers including additional routes to bicyclo[2.1.1]

hexanes are summarized as references 1 through 5 in the bibliography for this chapter.

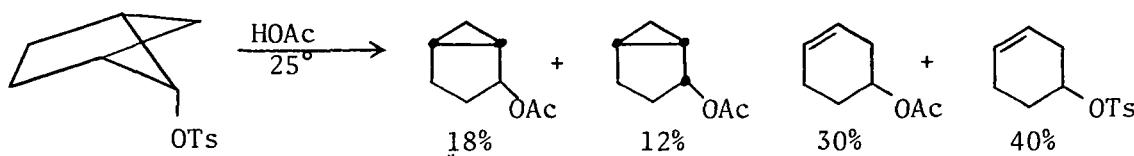
Thermal decomposition of bicyclo[2.1.1]hexane in the gas phase has been carried out by Srinivasan.⁷ The only detectable product at 327 to 366°C was 1,5-hexadiene. The reaction followed a first order rate law.

A study of hydrogen abstraction of bicyclo[2.1.1]hexane has been conducted by Srinivasan and Sonntag.⁸ They used methyl radicals as the hydrogen abstracting agent. A high degree of selectivity for abstraction of hydrogen from the number 2 position was observed.

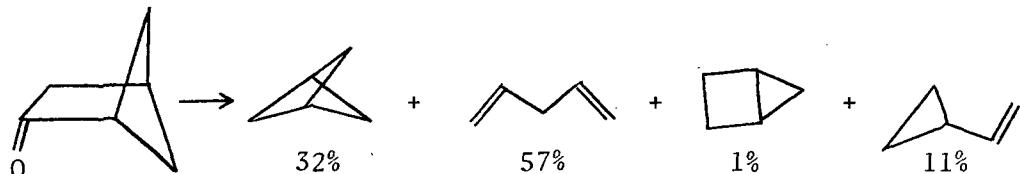
Meinwold and coworkers have studied the solvolysis of 2-substituted bicyclo[2.1.1]hexanes. Their studies have shown a marked rate enhancement compared with suitable reference models. On this basis they proposed that a non-classical carbonium is involved as an intermediate.



Wiberg¹⁰ has studied the solvolysis of 5-substituted bicyclo[2.1.1]hexanes. He concluded that the solvolysis reaction involves a concerted rearrangement mechanism

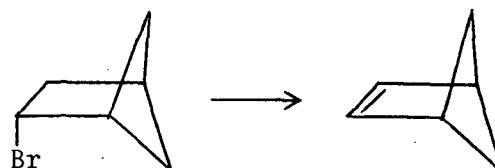


Solution photochemistry of bicyclo[2.1.1]hexane-2-one produced¹¹ bicyclo[1.1.1]pentane (32%), 1,4-pentadiene (57%), bicyclo[2.1.0]pentane (1%), and vinylcyclopropane (11%).

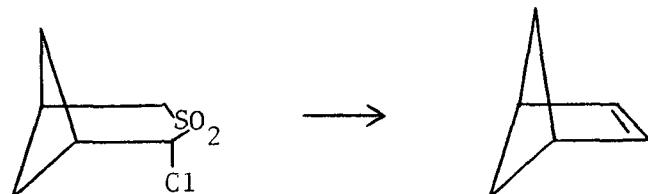


Bicyclohexenes

Bicyclo[2.1.1]hexenes have also been used in the study of strained ring systems: They are generally made by first synthesizing a bicyclo[2.1.1]hexane followed by insertion of the double band.¹²

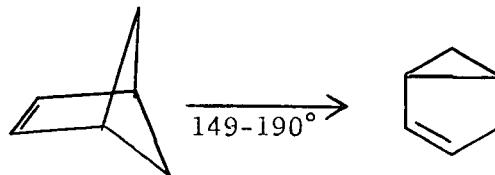


Solvolysis and carbonium ion rearrangement of other bicyclohexanes has also been used.¹³ Recently, a new route involving the Ramberg-Bäcklund rearrangement has been developed.¹⁴

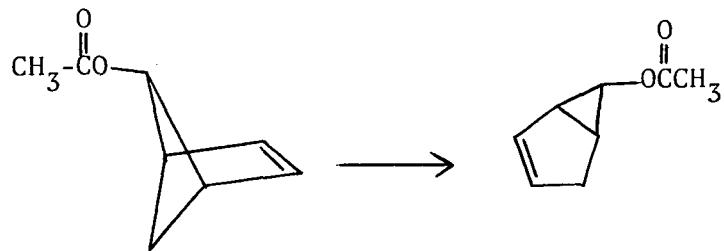


In this procedure, the double bond is inserted at the same time that the ring is formed.

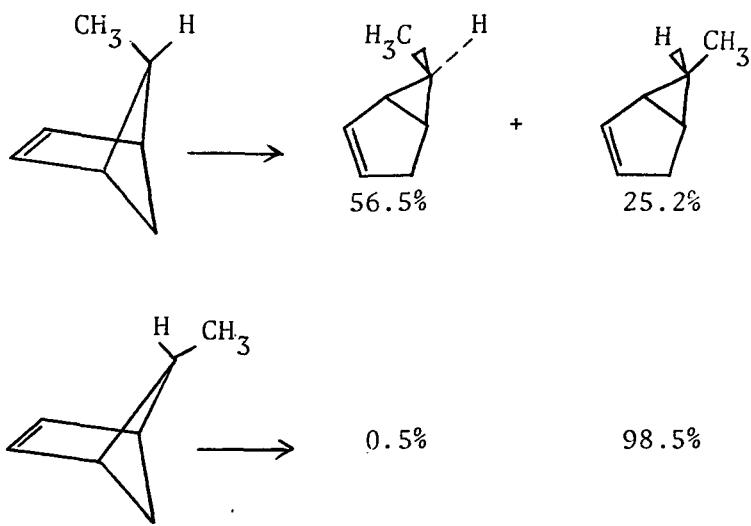
Thermal decomposition of bicyclo[2.1.1]hexene has been studied by Frey, Hopkins, and O'Niel.¹⁵ The reaction occurs readily between 149 and 190°C to produce bicyclo[3.1.0]hex-2-ene in quantitative yield following a first order rate law.



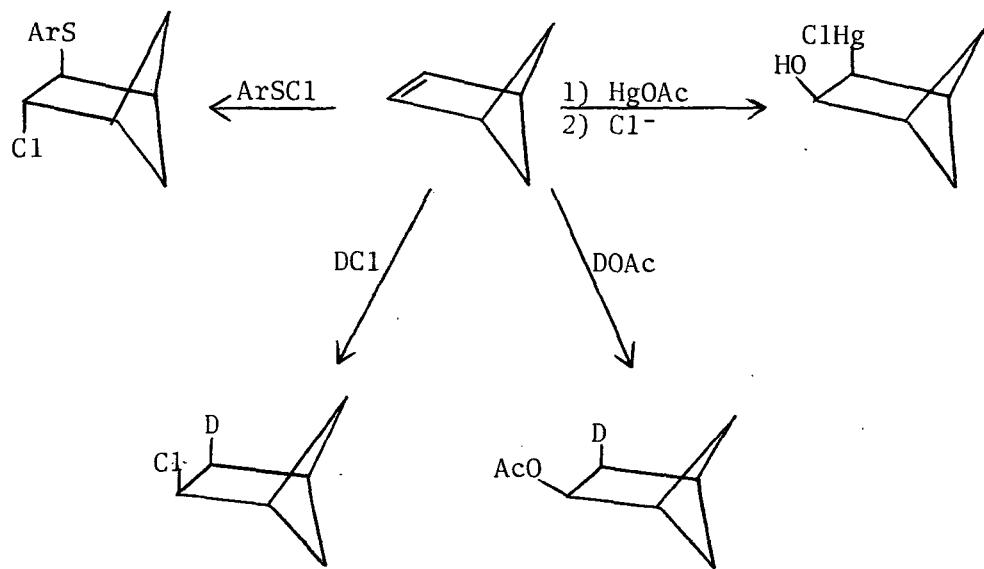
A concerted reaction mechanism was proposed. Thermolysis of bicyclo[2.1.1]hex-2-en-5-ol derivatives gave similar results.^{13a}



This reaction was interpreted as a suprafacial[1,3]sigmatropic rearrangement. The rearrangement was shown to be stereospecific when an endomethyl group was placed on the five position.¹⁶

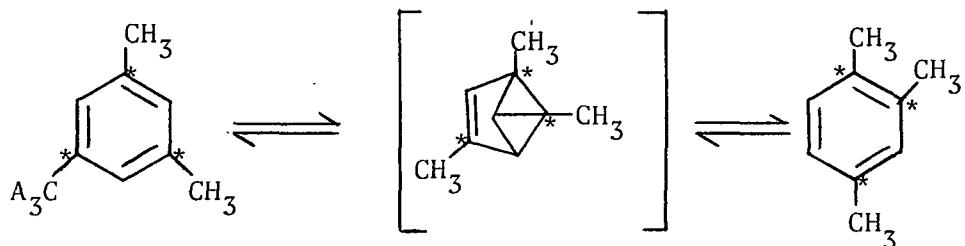


A study of the addition reactions of bicyclo[2.1.1]hex-2-ene suggests that in general, cis addition is the rule.¹⁷



Benzvalene

Photolysis of dialkylbenzenes has been reported to lead to isomerization.¹⁸ Thus, photolysis of o-xylene at 250 nm. gave a mixture of ortho, meta, and para xylenes. The major product could be explained by a 1,2 shift. Isotopic labeling experiments showed that a skeletal rearrangement of the benzene ring occurred.¹⁹ For example, mesitylene-1, 3,5-C¹⁴ gave 1,2,4-trimethylbenzene-1,2,4-C¹⁴ on irradiation at 253.7 nm. Benzvalene was proposed as an intermediate in the reaction.



Later,²⁰ photolysis of 1,3,5-tri-*t*-butylbenzene was shown to produce the corresponding benzvalene, Dewar benzene, and prismane. The yields in the photostationary mixture are summarized in figure 2-1.

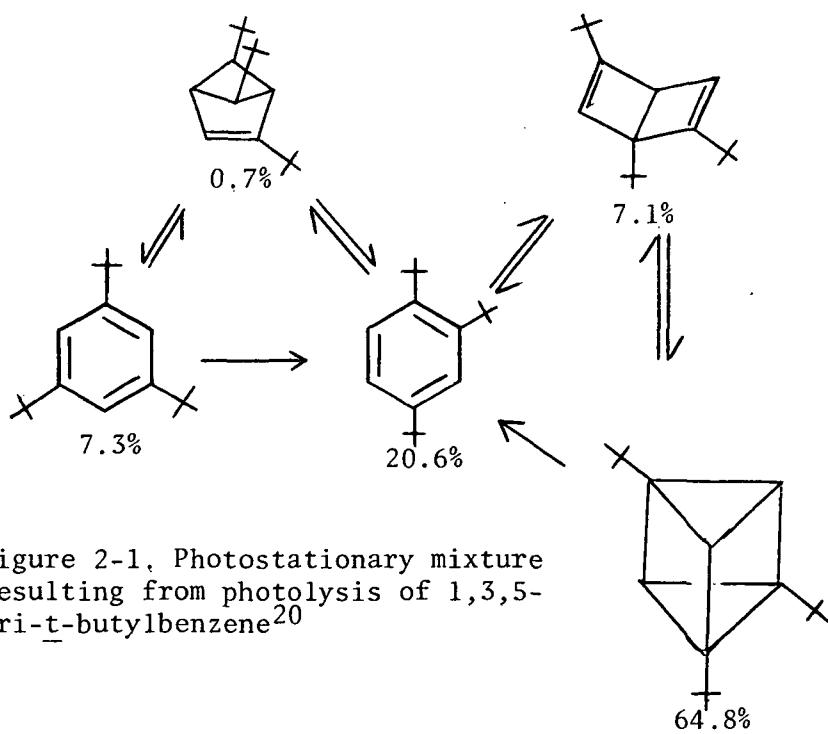
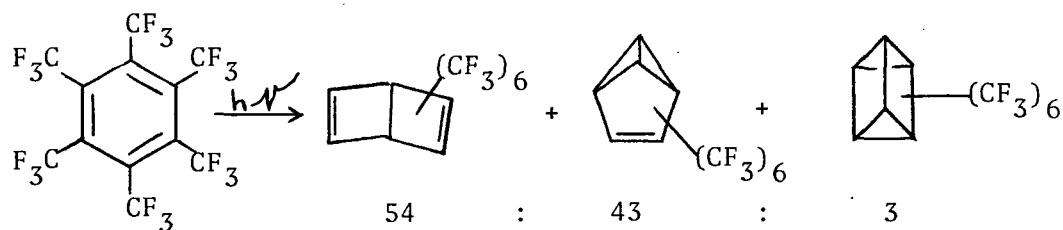


Figure 2-1. Photostationary mixture resulting from photolysis of 1,3,5-tri-*t*-butylbenzene²⁰

Irradiation of hexakis (trifluoromethyl) benzene was reported to give similar products.²¹



The product ratio was significantly changed, however.

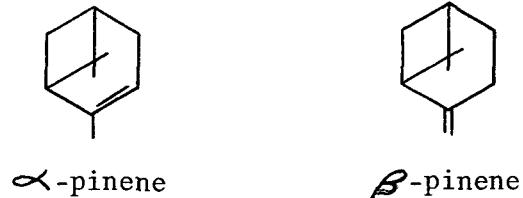
The isolation of unsubstituted benzvalene was finally reported²² in 1967. Rearomatization was reported to be slow at room temperature.

Bicycloheptanes

In contrast to the smaller bicyclic compounds, the bicycloheptanes are generally stable. In fact, they often exhibit unusual stability. The bicyclo[2.2.1]heptanes in particular show a remarkable degree of stability.

Bicyclo[3.1.1]heptane

The bicyclo[3.1.1]heptane ring system is readily available from naturally occurring α - and β -pinene.

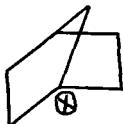


These compounds are used extensively in the paint industry where they are the principal constituents of turpentine. Since they are natural products, they will not be discussed further here. Specific, unusual applications are included later where appropriate.

Bicyclo[2.2.1]heptane

The bridgehead position in the bicyclo[2.2.1]heptanes has been found to be unusually stable toward nucleophilic substitution.²³ For example, 1-chloro-7,7-dimethylbicyclo[2.2.1]heptane has been reported²⁴ to be unreactive toward silver nitrate in aqueous ethanol. Furthermore, no chloride ion was observed when this compound was heated with 30% potassium hydroxide in 80% ethanol for 21 hours. These latter conditions were vigorous enough to dissolve the flask even though the bicyclic compound was inert.

This phenomenon has generally been explained in terms of the S_N1 and S_N2 reaction mechanisms. Backside attack of the nucleophile at the reaction center is required by the S_N2 reaction mechanism. This is impossible with bicyclo[2.2.1] octane and similar compounds. A carbonium ion is required in the S_N1 mechanism. A carbonium ion, however, has a strong tendency to have the groups attached to it be planar because of its orbital hybridization (sp^2). Bicyclo[2.2.1] heptane is too small, however, for the formation of a planar carbonium ion at the bridgehead position.



Bartlett and Knox²⁴ estimated the strain energy for a carbonium ion at the bridgehead of bicyclo[2.2.2]octane to be 22.5 kcal and suggested that for the bicyclo[2.2.1]heptane system it should be much higher.

In contrast to carbonium ion reactions, reactions of bicyclo[2.2.1] heptane which involve free radicals and carbonium ions proceed without undue

difficulty provided there is no steric inhibition toward resonance.²³

Free radical hydrogen abstraction, however, is inhibited at the bridgehead position. Koch and Gleicher,²⁵ for example, studied hydrogen abstractions from a series of polycyclic hydrocarbons. Using trichloromethyl radical as the radical source, they found no bridgehead hydrogen abstraction from bicyclo[2.2.1]heptane. Their observations for other hydrocarbons are summarized in Table 2-1. Normally, a tertiary position is highly reactive toward hydrogen atom extraction.

Table 2-1. Free radical hydrogen abstraction from bridgehead carbon atoms.²⁵

Bridgehead reactions	
Bicyclo[2.2.1]heptane	0%
Bicyclo[2.2.2]octane	8.8 ± 2%
Bicyclo[3.2.1]octane	Undeterminable
Bicyclo[3.3.1]nonane	100%
Adamantane	86.0 ± 2%
Homoadamantane*	73.5 ± 2%

*Reaction only at the 3 position. No reaction at the 1 position.

The entire subject of bicyclic activity was reviewed by Applequist and Roberts²³ in 1954.

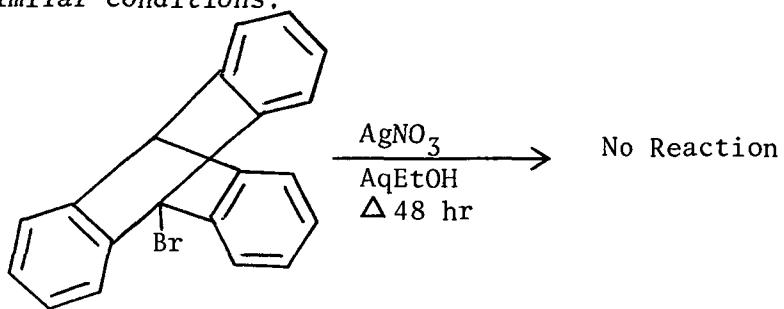
Bicyclooctanes

Owing to their somewhat larger size, bicyclooctanes are somewhat more reactive than bicycloheptanes. The bridgehead position is still quite unreactive, however.

Bicyclo[2.2.2]octane

1-Bromobicyclo[2.2.2]octane has been shown to be about 10^6 times less reactive than tertiary-butyl bromide toward nucleophilic substitution.²³

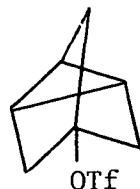
While this is faster than bicycloheptane, it is still a very slow reaction. The addition of fused benzene rings to the bicyclic system decreased the reactivity by making the compound more rigid.²⁶ Thus, 1-bromotriptycene was unreactive toward silver nitrate in aqueous ethanol and similar conditions.



The explanation for the lack of reactivity in this system is similar to that for the bicyclo[2.2.1]heptanes. Resonance stabilization of the carbonium ion is not possible because of the Bredts Rule.

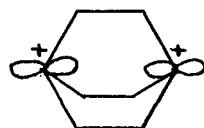
Bridgehead Reactivity

The determination of the relative reactivity of bridgehead systems is difficult because bridgehead compounds tend to be highly unreactive toward nucleophilic substitution. The reactivity of these compounds has been increased somewhat by using more reaction leaving groups. The most reactive leaving group found to date is the trifluoromethane-sulfonate group, abbreviated triflate (Tf). Using this leaving group, it has been found that the least reactive bicyclic compound toward nucleophilic substitution is nortricycyl triflate.²⁷

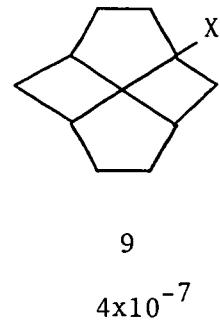
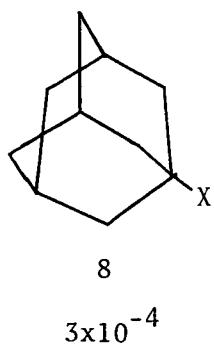
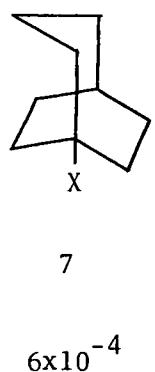
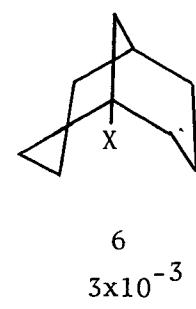
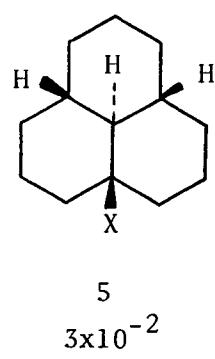
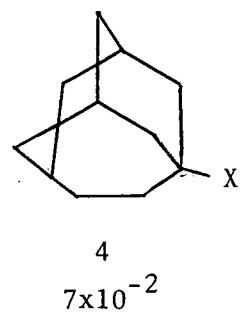
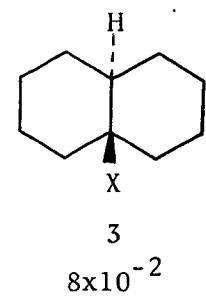
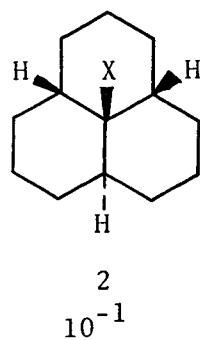
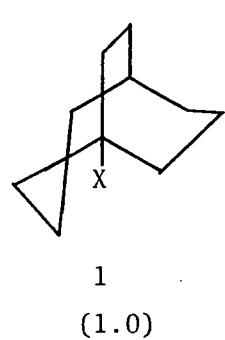


Bingham and Schleyer²⁸ have taken a mathematical approach to the problem. The results of their calculations on sixteen bicyclic compounds are summarized in figure (2-2). The least reactive compound is the nortricyclene derivative, as already observed.

Olah and coworkers²⁹ have prepared the 1,4-bicyclo[2.2.2]octyl dication.



The ion was found to be unusually stable. Nuclear magnetic resonance, molecular mechanical and MINDO/3 techniques were used to explain the stability.



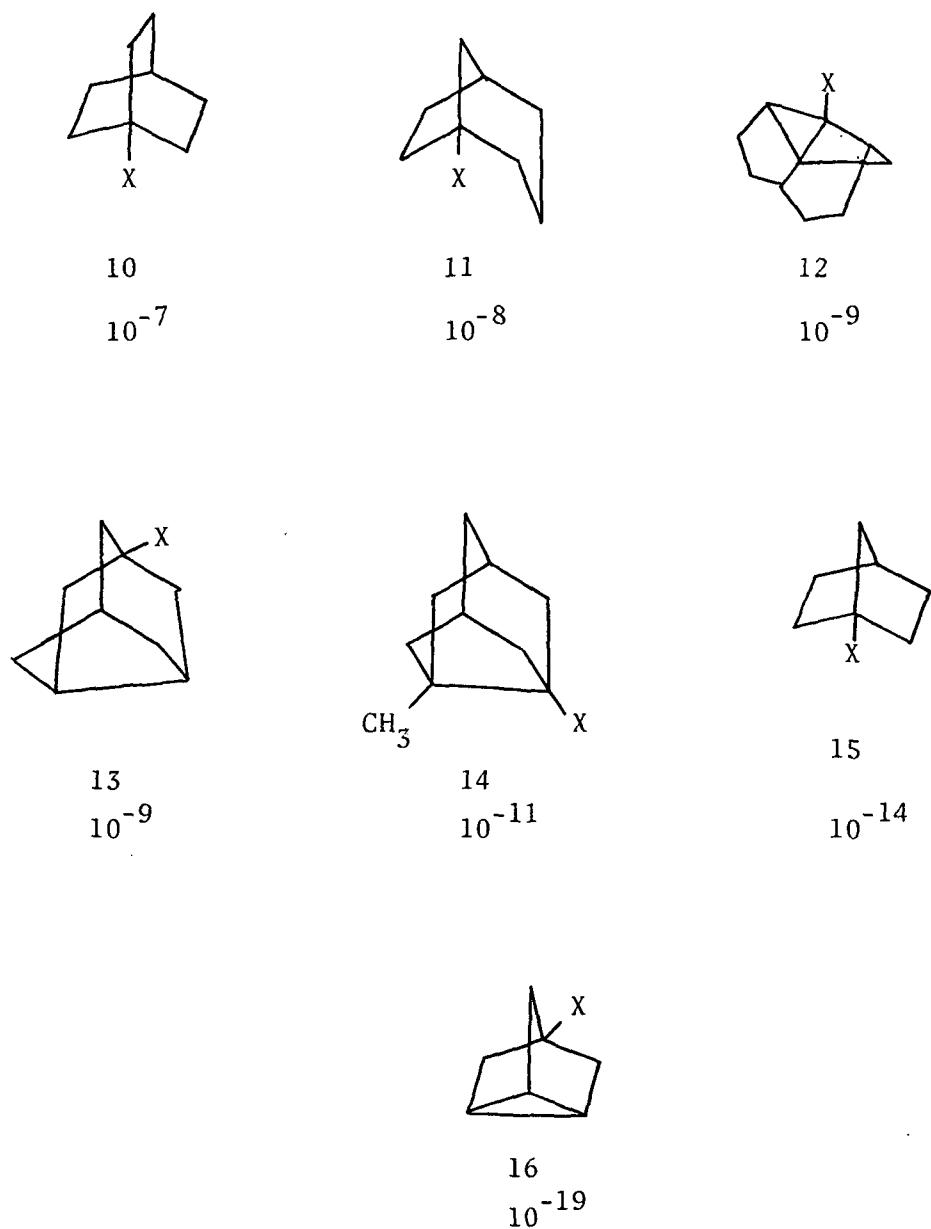


Figure 2-2, Relative carbonium ion reactivities of selected bicyclic compounds as calculated by Bingham and Schleyer.²⁸

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CHAPTER 2

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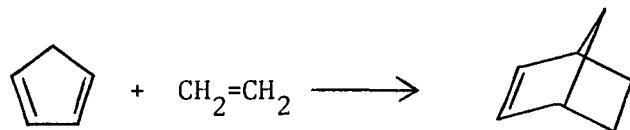
Chapter 3 - Synthetic Routes
to Bicyclic and Cage Compounds

As may be seen from the size of this report, a large number of bicyclic and cage compounds are known. Synthetic techniques leading to these compounds are varied. The purpose of this chapter is to outline some of the common techniques for synthesizing the major bicyclic systems. In particular, emphasis has been placed on the bicycloheptane, bicyclooctane and adamantane systems.

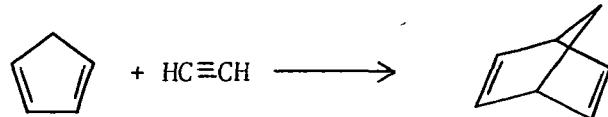
This is not an exhaustive treatment. Synthetic routes to specific compounds that have been discussed elsewhere may be found by referring to the reference for that compound.

Bicyclo[2.2.1]heptanes

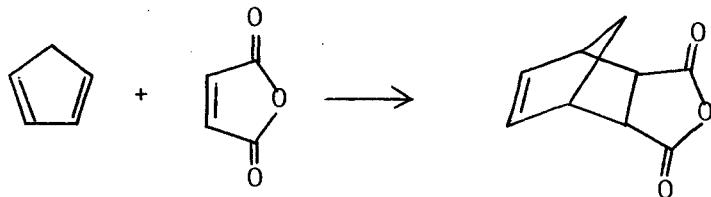
The general route to bicyclo[2.2.1]heptanes involves a 4+2 cyclo-addition of cyclopentadiene to ethylene or



acetylene derivatives,

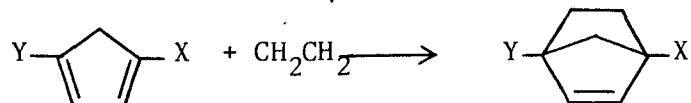


A common olefin that has been employed is maleic anhydride.

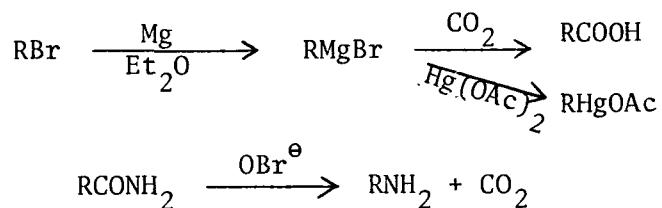


Many examples of compounds prepared in this manner are found throughout this report.

To place functional groups at the bridgehead position, it is necessary to start with the functional group on the 1 or 1 and 4 positions of the cyclopentadiene molecule.

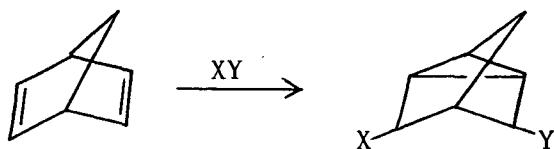


Once the bridgehead carbon atom has a functional group attached, it may be converted into another functional group by reactions involving a free radical or carbanion. Some examples that have been used are:



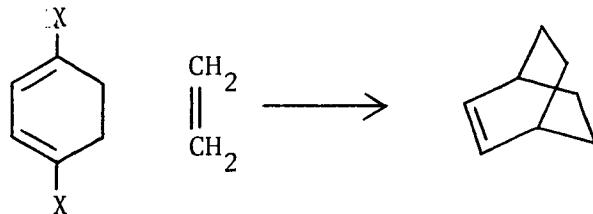
Reactions involving carbonium ions generally do not work well.

Nortricyclenes are made by 1,4 addition to bicyclo[2.2.1]hepta-2,5-diene.¹



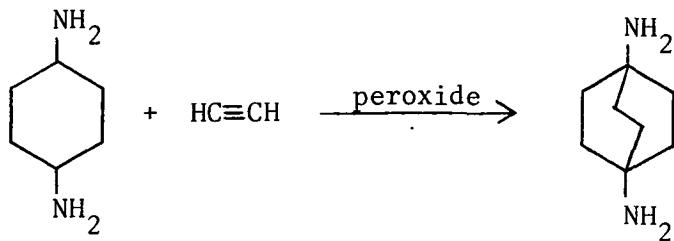
Bicyclo[2.2.2]octanes

Like the bicycloheptanes, the bicyclooctanes are usually made by a 4+2 cycloaddition reaction. Bridgehead substituents may be added

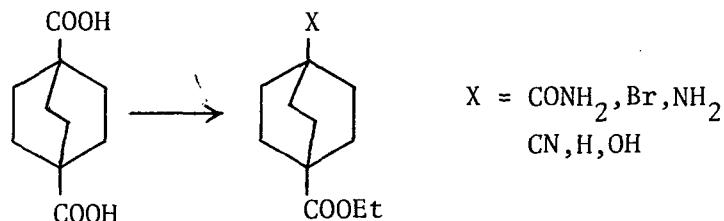


by starting with a 1,4-disubstituted cyclohexane.

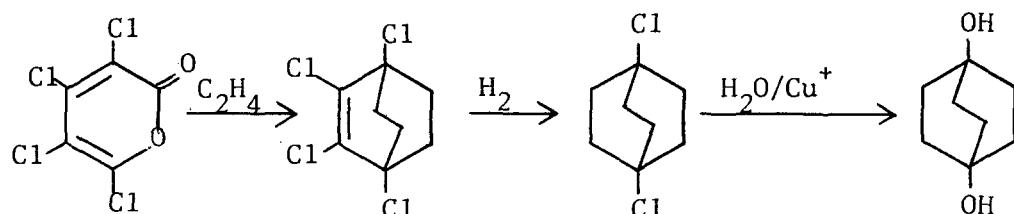
1,4-Diamino[2.2.2]bicyclooctane has been made by treating 1,4-diaminocyclohexane with acetylene in the presence of ditertiary butyl peroxide.²



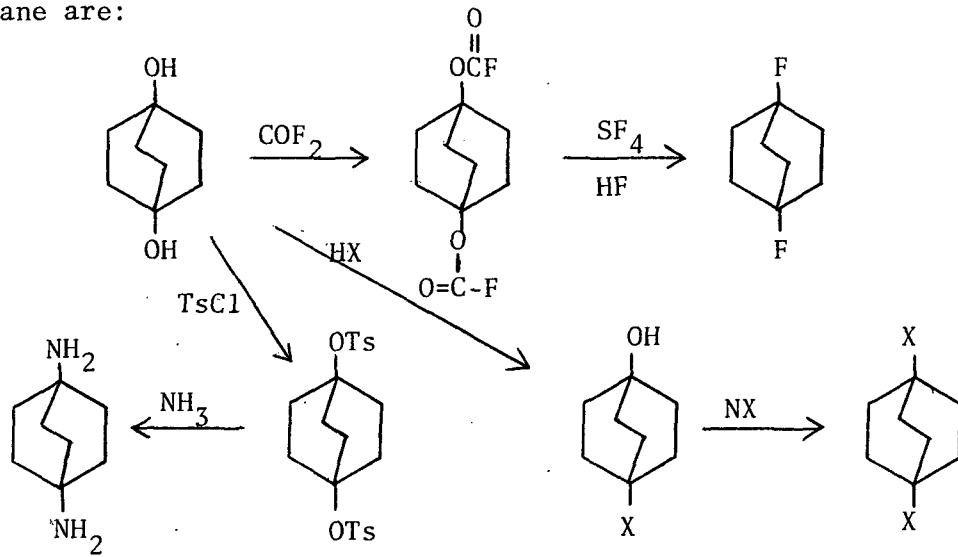
Bicyclo[2.2.2]octane-1-carboxylic acids containing substituents in the 4-position have been synthesized from the corresponding 1,4-dicarboxylic acid ester.^{3a}



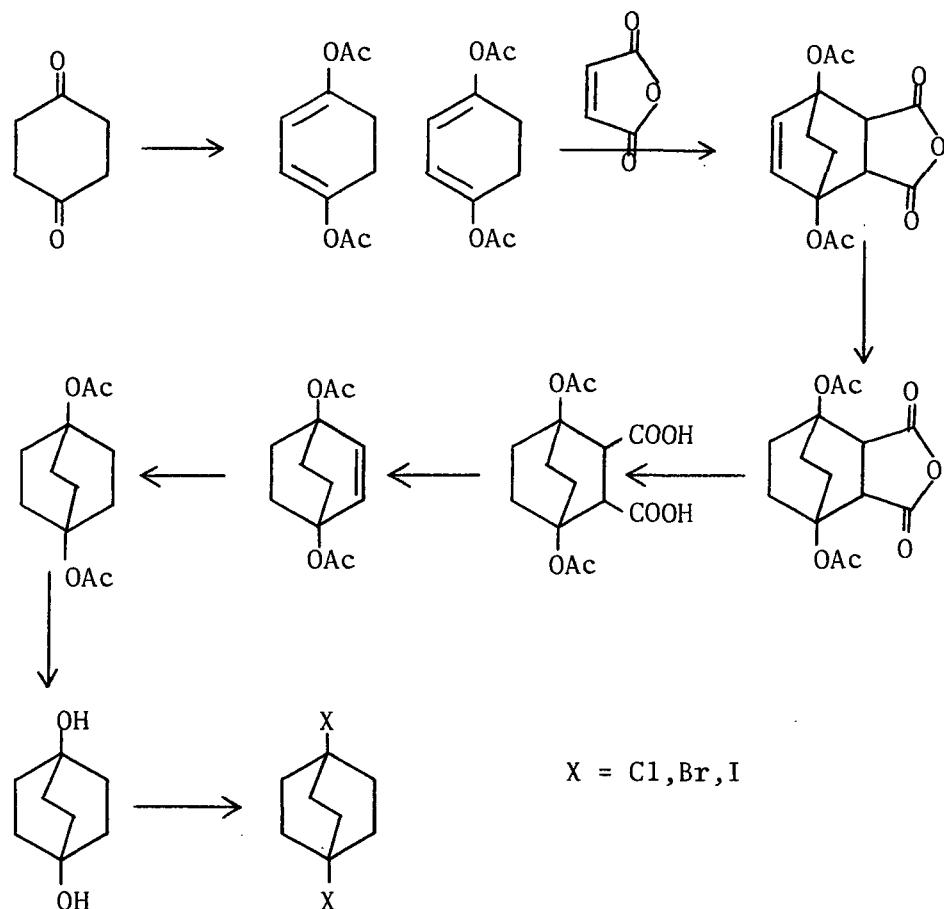
1,4-Dihydroxybicyclo[2.2.2]octane has been prepared by the following sequence:⁴



Some compounds that have been derived from 1,4-dihydroxybicyclo[2.2.2]-octane are:



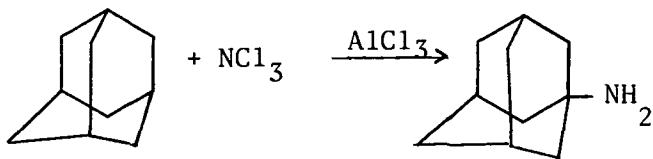
The following sequence of reactions has also been reported.⁵



Adamantanes

The easiest way to make adamantane is to isomerize endo-trimethyl-
enenorbornane (obtained by hydrogenation of dicyclopentadiene) with
aluminum chloride or another Lewis acid.⁶ Polymethyladamantanes have
been made by treating perhydro tricyclic aromatic hydrocarbons in a
similar manner.⁷ 1,3,5,7-tetrasubstituted adamantanes, particularly
the tetramethyl product have been specifically reported.⁸

1-Aminoadamantane is an important antiviral compound. Its synthesis
has been described by several authors.⁹ One route involved the addition
of nitrogen trichloride to adamantane in the presence of aluminum
chloride.^{9a}



1,3-Dibromoadamantane has been prepared by reaction of adamantane or
1-bromoadamantane with bromine and aluminum bromide.¹⁰ Polyhaloadaman-
tanes have been made in a similar manner.¹¹

Bromination, chlorination, sulfonation, hydroxymethylation, nitra-
tion and air oxidation of adamantane have been studied by Smith and
Williams.¹² A high degree of selectivity for attack at the tertiary
position was observed.

Bingham and Schleyer¹³ have looked at the chromic acid oxidation of
bridgehead compounds. While bicycloheptane and bicyclooctane reacted

slowly, attack at the bridgehead position of adamantane was considered to be sufficiently rapid and selective that the method could be synthetically useful.

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Chapter 4 - Theoretical Applications of Bicyclic and Cage Compounds

The three-dimensional structures of bicyclic and cage compounds makes them ideally suited for many theoretical studies. As a consequence, they have been used extensively in studies related to bonding in organic chemistry.

Studies of Strained Bonds

Bicyclic and cage compounds containing small rings have considerable ring strain. As a consequence, they tend to show unusual reactivity. This unusual reactivity has made them the subject of numerous studies of ring strain and strained bonds. Some of these studies have been summarized in Chapter 2. Major workers in this field have been Wiberg¹ and Meinwald.² This area has grown to the point that a thorough review by a neutral observer might be useful.

Studies of Carbonium Ions

As indicated in Chapter 2, bicycloheptanes and bicyclooctanes form carbonium ions at the bridgehead only with difficulty. Studies of bridgehead carbonium ion reactions have added significantly to the knowledge of the shape of carbonium ions and their reactivity. While a planar carbonium ion is predicted by quantum mechanics, the extent of the tendency for carbonium ions to achieve a planar configuration, as discussed in Chapter 2, probably could not have been predicted without the laboratory studies.

Carbonium ions formed at positions other than the bridgehead do not show the unusual lack of reactivity associated with bridgehead carbon atoms. On the contrary, they often show unusual reactivity, stereo-

chemistry, and a tendency to undergo rearrangement reactions. These phenomena have been rationalized by introducing the concept of non-classical carbonium ions. This concept has been argued and reviewed many times in the last fifteen years or so, and will not be discussed here. The main protagonists in the area have been H. C. Brown, S. Winstein, D. J. Cram, and J. Roberts, although others including P. v. R. Schleyer and G. Olah have also become involved. A few key reviews are found in reference 3.

Bredt's Rule

Bredt,⁴ a specialist in camphor chemistry, suggested a rule relating to bicyclic compounds in 1924 that has since come to bear his name. In its most simple form, Bredt's Rule states that a double bond cannot exist at the bridgehead position of a bicyclic compound unless the rings are large enough to accommodate it without excessive strain.

Since that time, much effort has been expended to define the limits of the rule. Fawcett⁵ reviewed the subject in 1950 and suggested that in three-dimensional systems a double bond at the bridgehead position should be isolable if the sum of the atoms between the bridges is greater than or equal to nine. This number was call the S value. Transient intermediates were believed to be possible for S as low as six.

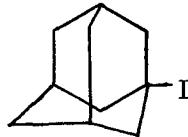
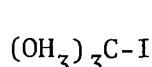
This concept proved to be fairly accurate, and the subject rested at this point until 1967 when Wiseman⁶ prepared bicyclo[3.3.1]non-1-ene and suggested a refinement of the rule. Wiseman postulated that the compound should be isolable if the largest ring contains at least eight carbon atoms, and if the olefin is trans to the largest ring. He further

postulated that compounds containing a trans cycloheptene ring might be found as transient intermediates. Since that time, the hypothesis has been substantiated⁷ by evidence suggesting the transient existance of bicyclo[3.2.2]non-1-ene.

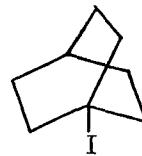
The subject was reviewed by Kobrich⁸ in 1973. The entire topic was reviewed again in 1974 by Buchanan.⁹

Studies of Free Radicals

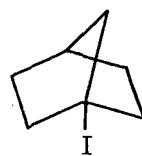
Free radicals normally attack tertiary positions preferentially. As indicated in Chapter 2, however, the bridgehead positions in bicycloheptanes are unreactive toward free radical attack. Danen, Tipton, and Saunders¹⁰ studied the relative rate of abstraction of iodine from compounds (4-1), (4-2), (4-3), and (4-4).



(4-1)



(4-2)



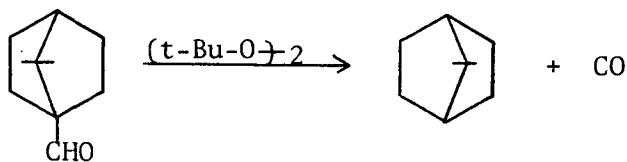
(4-3)

(4-4)

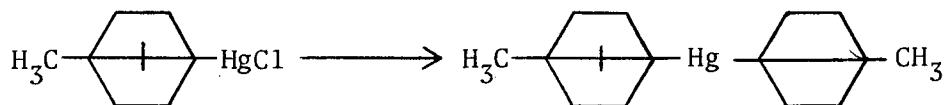
The relative order of stability was found to be (4-1)>(4-2)>(4-3)>(4-4).

The observation that free radicals may exist at the bridgehead position has been used as evidence for the free radical nature of some

reactions.¹¹ Decarbonmonoxylation is one example,



The reduction of 4-camphylmercuric chloride with sodium stannite is also believed to involve a free radical intermediate.



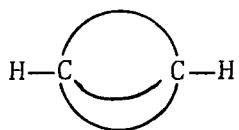
Carbanion Reactions

Reactions involving carbanions have not been as well studied as those involving carbonium ions. Nevertheless, it is generally accepted that a carbanion consists of a rapidly inverting sp^3 species.¹² Bridgehead positions should have no problems with carbanion formation except for inhibition to inversion.

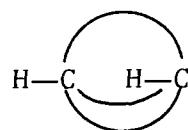
This situation is generally true. Reactions which tend to proceed via carbanion intermediates generally proceed without undue difficulty. Reactions which might be included in this category are Grignard and other organometallic reactions, and the Hoffman Rearrangement. These reactions are useful for interconversion of functional groups at the bridgehead position.

In-Out Isomerism

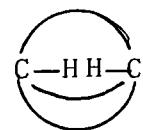
Most bicyclic compounds have the bridgehead substituents located outside the hydrocarbon cage. Small rings, of course, cannot exhibit this phenomenon. Larger rings, however, can exist in three forms, out-out, out-in, and in-in.



out,out

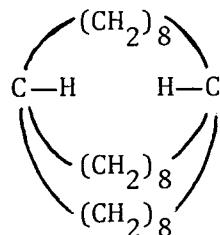


out, in

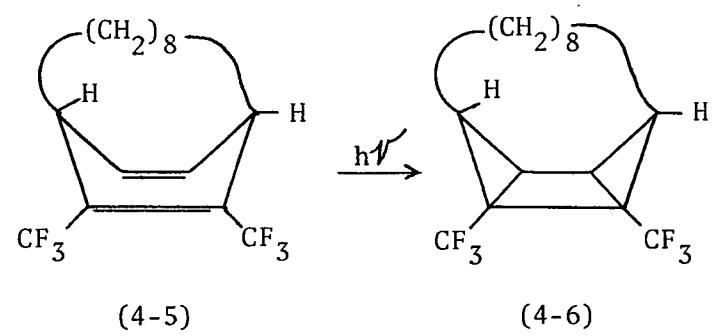


in,in

There has not been a great deal of work on this phenomenon, but a few compounds have been made. In particular, bicyclo[8.8.8]hexacosane has been prepared in the in-in form.¹³



For this size ring system, it was suggested that the in-in form was the most stable form of the molecule. Gassmann and Thummel¹⁴ in a companion paper, prepared (4-5) and (4-6).



REFERENCES

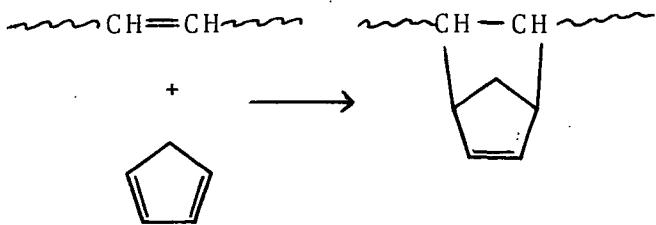
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2. For the key references to the work of J. Meinwold in this area, see the reference section of Chapter 2.
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Chapter 5 - Applications to Polymers

At the research level, bicyclic and cage compounds have been used rather extensively for polymers. Most of the common bicyclic and cage systems have been synthesized and incorporated into polymers. Polyamides and polyesters have probably received the most study, but bicyclic analogs of the other common polymer types, such as polyolefins, polyvinyls, polyethers, and polyurethanes have also been prepared. These compounds are generally reported to have improved physical properties such as thermal resistance.

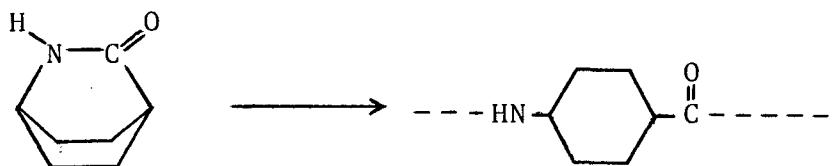
The general procedure for making polymers containing bicyclic groups has involved synthesis of the appropriate monomer followed by a classical polymerization process. Two alternate routes have also been used in selected cases, however, which might find more extensive use. In the first route, a preformed polymer containing a double bond is treated with a cyclic diene to form bicyclic groups along the polymer chain by a 4 + 2 cycloaddition reaction.



This should be a good way to incorporate flame retardancy into the polymer by using compounds like hexachlorocyclopentadiene as the diene. The disadvantage of this procedure is that there is no assurance that all of the olefinic sites in the polymer will be reacted.

A more certain technique that assures that all sights are reacted involves formation of the bicyclic compound as part of the polymerization process. This has been accomplished in one instance by treating a diimide containing a double bond at two sights with a cyclopentadiene. The resulting cycloaddition product was a polymer containing a bicyclo-[2.2.2]octane ring system as an integral part of the molecule.

In an alternate route to polymers, bicyclic lactams, lactones, and similar compounds have been used as monomers. The resulting polymer does not contain a bicyclic ring, however, even though the monomer was bicyclic.



In spite of the extensive research work on bicyclic polymers, and the improved properties that they are reported to have, it is not obvious that they have found any appreciable commercial market. This situation is probably due to the high cost of the bicyclic monomers. Only highly desirable and unusual properties could justify using an expensive polymer, and a significant, high volume market probably could not be developed.

Polyamides

Polyamides are the main, but not the only, topic of one of the most extensive patents in the area of bicyclic polymers.¹ Polyamides, polyesters, polyureas, and polyurethanes made from bridgehead substituted bicyclo-[2.2.1]heptanes, bicyclo[2.2.2]octanes, bicyclo[3.2.2]nonanes, bicyclo-[3.3.1]nonanes, adamantanes, and related bicyclic compounds are disclosed in this patent. These polymers are reported to have improved mechanical

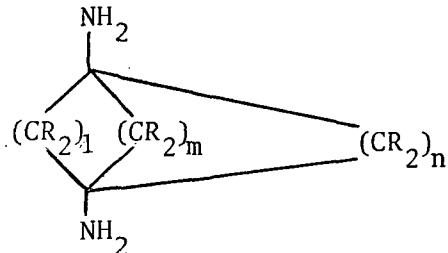
properties including thermal and oxidative stability. Their use in fibers was suggested, and data on fiber properties were included. Some specific polymers from the patent are listed in Table 5-1. Other related polymers

Table 5-1. Some specific polymers disclosed in U.S. Patent 3,301,827.

poly(bicyclo[2.2.2]oct-1,4-ylene sebacamide)
 poly(1-bicyclo[2.2.2]octylene-4-carbonamide)
 poly(bicyclo[2.2.2]oct-1,4-ylene suberamide)
 poly(bicyclo[2.2.2]oct-1,4-ylene isophthalate)
 poly(bicyclo[2.2.2]oct-1,4-ylene terephthalate)
 poly(bicyclo[2.2.2]oct-1,4-ylene-m-terphenyl-4,4"-dicarboxylate)
 poly(adamant-1,3-ylene sebacamide)
 polymer from adamantane-1,3-diisocyanate and
 polytetramethylene ether glycol (M.W. about 2000)
 polymer from adamantane-1,3-diisocyanate and
 1,3-diaminocyclohexane

are included in the patent, as well as synthetic routes to some of the monomers.

In related work, Martin² has patented heat and oxidation stable polyamides made from diamines of the type:

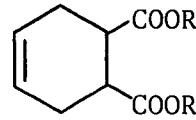
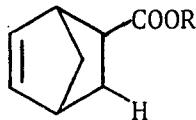


where 1, m, and n are 1, 2 or 3, and their sum is 5 to 9. The preferred

diamines were bicyclo[2.2.1]heptane-1,4-diamine, and bicyclo[2.2.2]-octane-1,4-diamine. The preferred diabasic acids were adipic acid, suberic acid, azelaic acid, sebacic acid, isophthalic acid, and terephthalic acid. In addition to the diamines, diols and amino alcohols are used to make polyesters and combination polyester-polyamides.

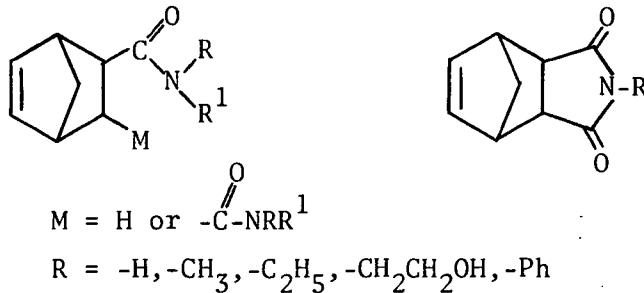
Bicyclo[2.2.1]heptanes

Acrylonitrile is reported³ to form an interpolymer with the following compounds:



R = alkyl group with 1-4 carbon atoms

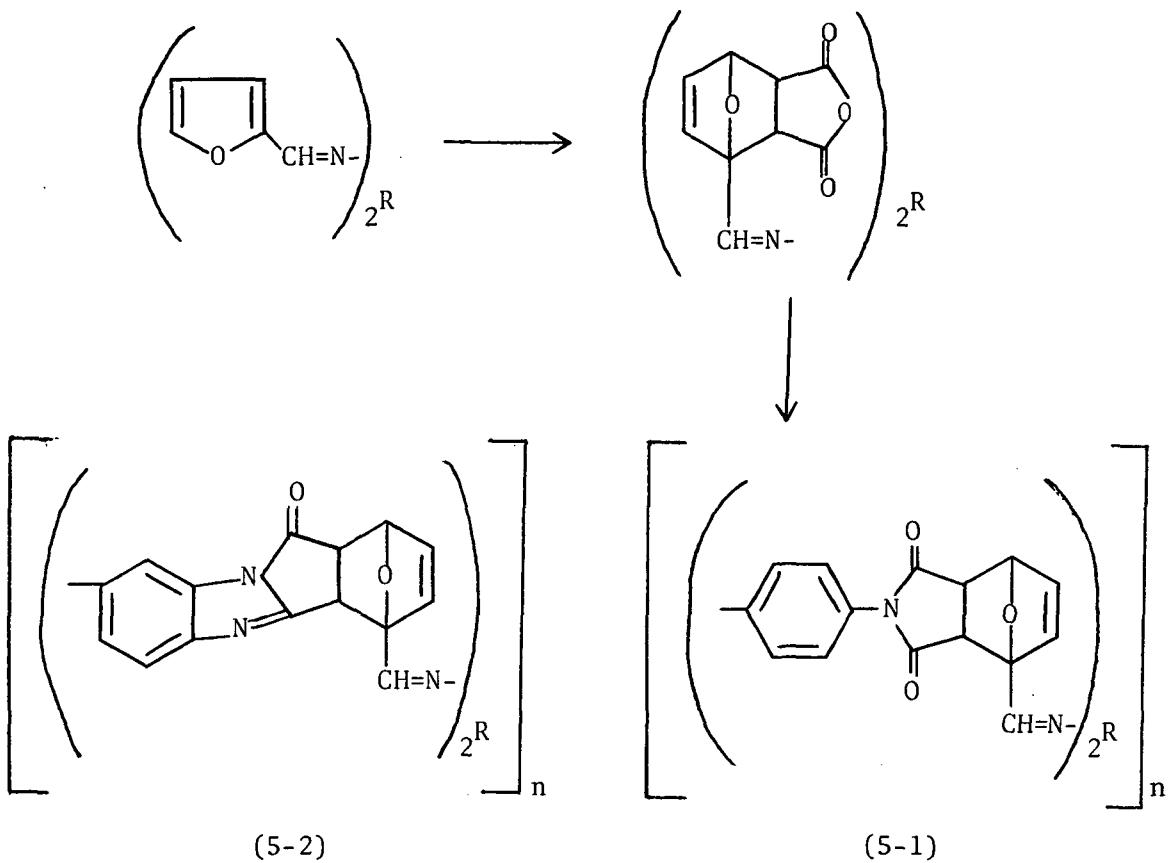
Similar polymers are made from the corresponding imide.⁴



These materials are reported to be outstanding for fiber formation.

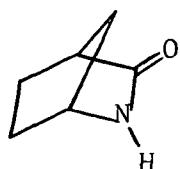
Bicyclo[2.2.1]heptane 2,3-dicarboxylic acid forms a polymer with tetramethylenediamine.^{4a} This polymer is also a good fiber forming material.

Bicyclic polyimides (5-2) and polyimidazoles (5-1) derived from furan have been used to make heat stable polymers.⁵



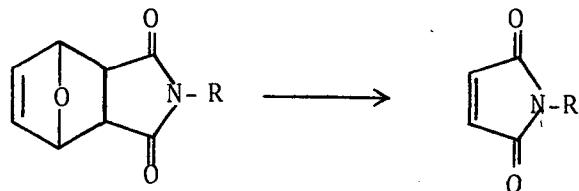
These polymers were reported to be stable up to 350-450° in air.

2-Azabicyclo[2.2.1]heptane-3-one has been used as a monomer for



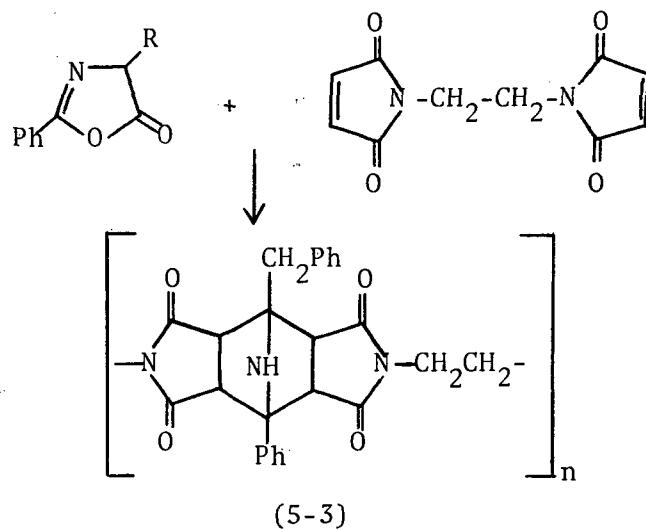
the formation of polyamides.⁶ In this case, the monomer is bicyclic, but the resulting polymer is not. There are several examples of this situation in the bicyclooctane systems discussed later in this chapter.

Another source of nonbicyclic polymers with a bicyclic origin is the maleimides. N-substituted maleimides for polymers have been prepared by the retro Diels-Alder (4 + 2 cycloaddition) reaction.⁷

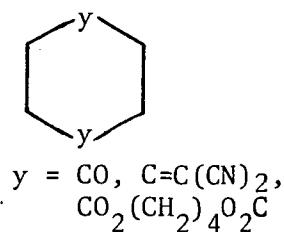
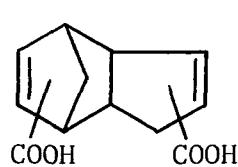


Insecticidal and fungicidal properties have also been attributed to some of these materials.⁸

Formation of the bicyclic systems during polymer formation has been achieved by carrying out a 1,3-dipolar addition between 5-oxazolone and nonconjugated dienes.⁹



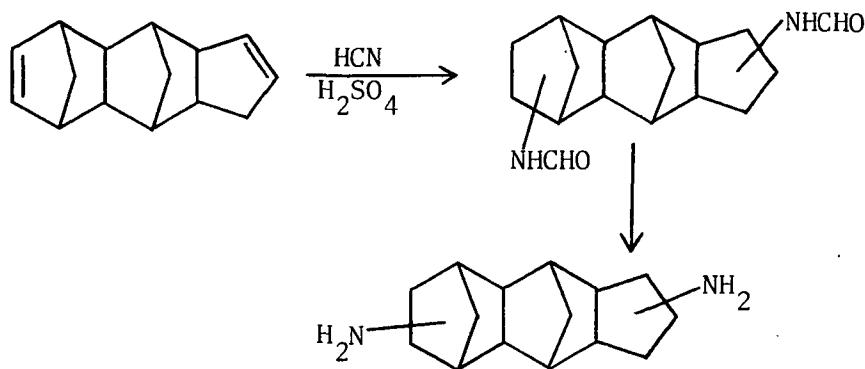
Other dienes that were used included the following:



These polymers were reported to have increased thermal stability.

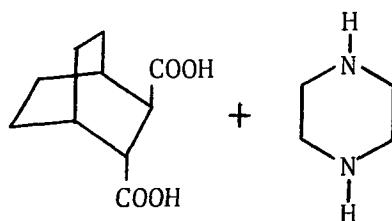
Application to coatings were suggested. Polymer (5-3) was reported to have a weight loss of 10% at 350°, 20% at 385°, and 50% at 500°.

Tricyclopentadiene has been used as a starting material for the formation of diamines for use in polyamides via the Ritter's reaction.¹⁰



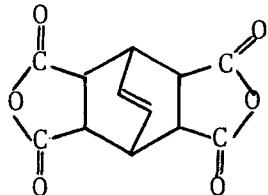
Bicyclo[2.2.2]octanes

Polyamides from bicyclo[2.2.2]octan-trans-2,3-dicarboxylic acid and piperazine were prepared by Overberger and coworkers¹¹ in order to study a structurally rigid, asymmetric polyamide that could not hydrogen bond.

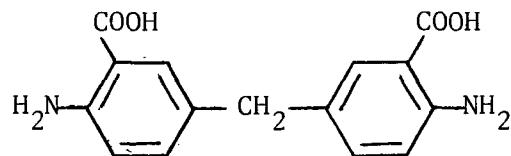


A discussion of the special properties anticipated for these materials was not included in the papers.

Bicyclo[2.2.2]oct-7-ene-2,3,5,6-tetracarboxylic acid dianhydride has been prepared by treating 3,5-cyclohexadiene-1,2-trans-dicarboxylic

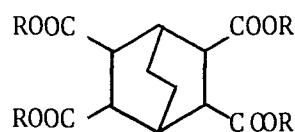


acid with maleic anhydride.¹² Heat resistant polyimides having high softening points and favorable electrical properties are made from this monomer and an appropriate diamine such as 4,4'-diaminodiphenylmethane.¹³ Lacquered coatings, molded articles, and film were proposed as uses for these materials. When 4,4'-diaminodiphenylmethane-3,3'-dicarboxylic acid was used as the diamine, the resulting polymer could be crosslinked



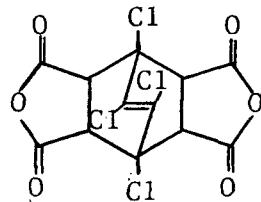
with toluene and diisocyanante to give an elastic crosslinked coating for wires.^{13d}

An alternate route to these polymers involves using the tetracarboxylic acid ester instead of the anhydride.¹⁴



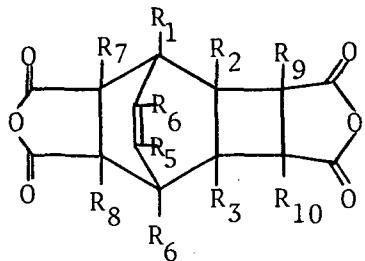
The saturated compound has also been prepared and used to make heat stable polyimides for protective coatings and building elements.¹⁵

Polymerization of 1,4,7,8-tetrachlorobicyclo[2.2.2]-7-octene-2, 3,5,6-tetracarboxylic dianhydride rubeanic acid to form a polymer suitable

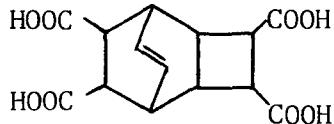


for use as a copy sheet for the thermographic copy process.¹⁶ Sheets made from this and other polymers reported in the patent are less subject to aging.

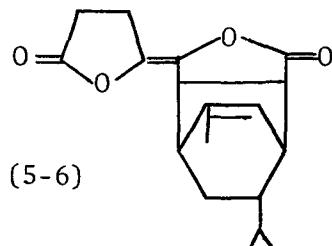
A few rather exotic bicyclic compounds have been used as monomers for polyamides, such as (5-4), (5-5), and (5-6).



(5-4)



(5-5)

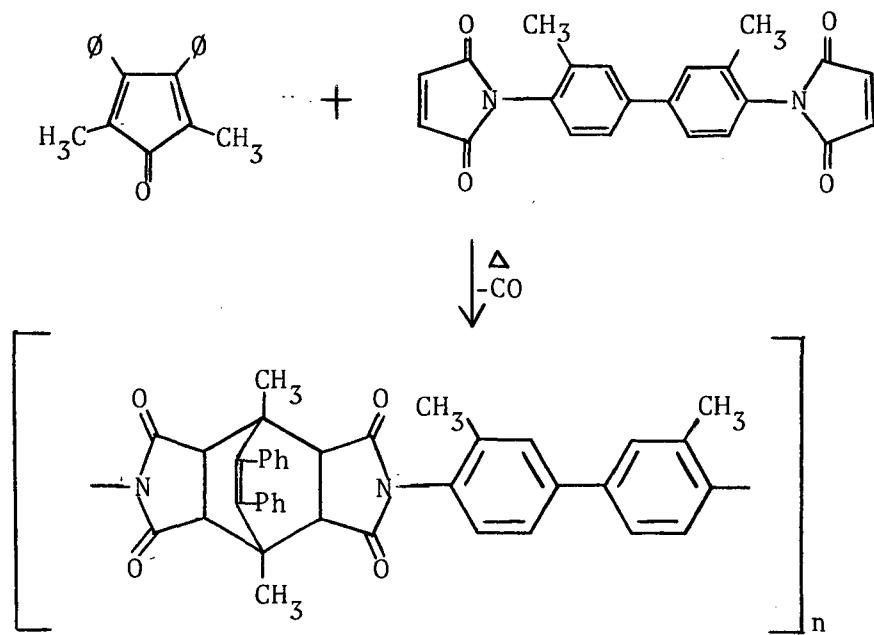


(5-6)

Polyimides derived from (5-4) are reported to have properties that are superior to polyamides.¹⁷ They are proposed for use as coatings and electrical insulation material. Compound (5-4) has been polymerized with both aliphatic and aromatic diamines¹⁸ to give polymers that showed heat resistance to 360°. Compound (5-6) is converted to a polyamide by reaction with hexamethylenediamine.¹⁹

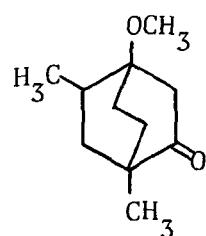
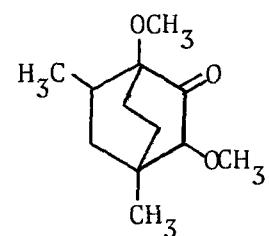
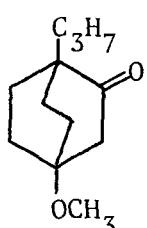
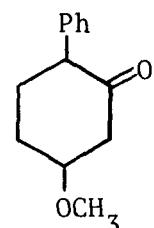
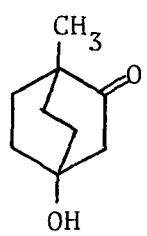
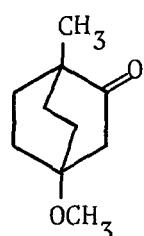
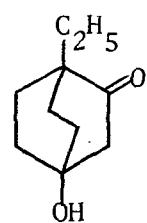
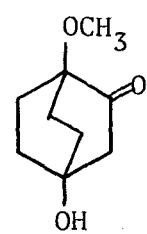
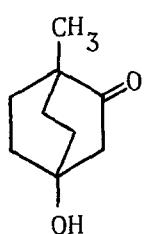
Another series of bicyclic polyamides is obtained by treating triethylenediamine (1,4-diazabicyclo[2.2.2]octane) with an appropriate carboxylic acid. Acids such as maleic anhydride,²⁰ phthalic anhydride,²¹ and linoleic dimer acid,²² or other higher fatty acids²³ have been used. The latter two compounds have been proposed as adhesives and potting resins respectively.

The formation of a bicyclooctane ring system during the polymerization process was reported by Kraiman.²⁴



This procedure has been used for similar polymers.²⁵

A series of substituted bicyclo[2.2.2]oct-2-ene compounds have been reported as intermediates in the production of heat resistant polyamides. The following compounds are specifically included.²⁶



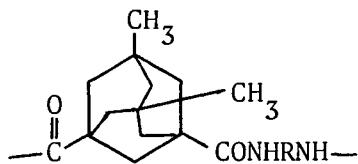
No details on how they were used were given in the patent abstracts.

Several monomers have been made that can be used to make polyamides. For example, 1,4-bis-(0-chlorobenzylamino)-bicyclo[2.2.2]octane²⁷ is a suitable diamine. Similar 1,4 disubstituted bicyclo[2.2.2]octanes containing amides.^{28,29} carboxylic acids²⁹ and amino groups³⁰ have been reported.

Adamantanes.

The adamantane ring has been incorporated into polyamides in several ways. Adamantan-1,3-dicarbonyl chloride has been polymerized with diamines by either interfacial or solution polymerization.³¹ Hexamethylenediamine, ethylenediamine, m-phenylenediamine, and 1,3-adamantyl-enediamine have been used. The products are reported to have good impact resistance, a low coefficient of friction, a high softening point, good tensil strength, and low water absorption.

1,3-Diamidoadamantanes have been prepared³² and found useful in the preparation of polyamides and as antistatic agents for fibers and moldings. Polyamides of this type are clear films and sheets. They are useful as wrappings, displays and in structural design. They may be drawn into fibers for textiles, carpeting, and tire cord.³³

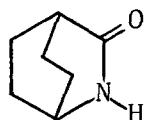


Nonbicyclic polyamides from bicyclic monomers.

Hall³⁴ carried out a study in 1958 to determine which bicyclic rings containing suitable functional groups (lactams, lactones, etc.) could be

induced to polymerize. In general, he found when bicyclo[2.2.2]octanes and bicyclo[3.2.2]nonanes containing a cyclohexane ring in a boat form are used that polymerization occurs readily. Bicyclo[3.2.1]octanes varied in polymerizability. When stable chair forms of cyclohexane were present as with bicyclo[3.3.1]nonane, no polymerization occurred.

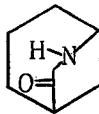
Since Hall's pioneering work in this area, several bicyclic monomers have been reported along with their corresponding polymers and copolymers. 2-Azabicyclo[2.2.2]oct-3-ane (5-7) has been used rather extensively to



(5-7)

make copolymers with ϵ -caprolactam.^{35,38} Fibers made from these copolymers are said^{35c} to exceed the quality of Nylon 6. Increased thermal and oxidative thermal stability were also reported.^{35g} A copolymer between (5-6) and the corresponding lactone (2-oxabicyclo[2.2.2]oct-3-ane) has also been reported.³⁶

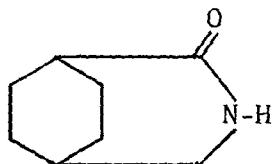
2-Azabicyclo[3.2.1]oct-3-ane (5-8) has also been used to prepare



(5-8)

polyamides.^{37,38} Use in fibers was suggested because of the ability of the polymer to absorb 6% water.³⁸

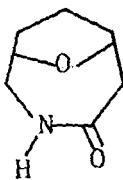
3-Azabicyclo[3.2.2]nonan-2-one (5-9) has also been prepared³⁹ for use in polymers.⁴⁰



(5-9)

The polymers have good chemical resistance, heat resistance and mechanical stability and are useful for machine parts, electrical parts, and tire cords.^{40a}

Attempted synthesis of the lactam (5-10) gave only polymer.⁴¹



(5-10)

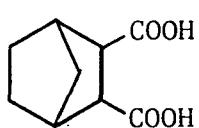
It was suggested that the ether group was cleaved in the acidic medium used in the synthesis.

Polyesters

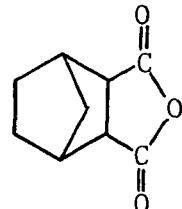
Like the polyamides, bicyclic polyesters have been studied rather extensively. Bicyclo[2.2.1]heptane and bicyclo[2.2.2]octane systems have been thoroughly studied. Adamantane has also been incorporated into polyesters.

Bicyclo[2.2.1]heptanes

The most common monomer of the bicyclo[2.2.1]heptane series that has been used in polyesters is bicyclo[2.2.1]heptan-2,3-dicarboxylic acid (5-11) and derivatives such as the anhydride. A copolymer made



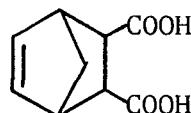
(5-11)



from the diethyleneglycol ester of (5-11), styrene, and maleic anhydride has been suggested for impregnation of textiles and as a casting resin.⁴² Other glycols were also used.

Copolymerization of a diester of (5-11) with vinyl chloride or vinylidene chloride in the presence of a peroxide catalyst gave a polymer with improved heat and light stability, and improved molding and extrusion characteristics.^{43a} A series of esters of (5-11) such as the octadienoate, crotonate, methacrylate and acrylate have been reported for use in paints, varnishes and coating compounds because they form tough films on exposure to air.⁴⁴

The corresponding compound containing a double bond at the number 5 position (5-12) has been used even more extensively, probably because

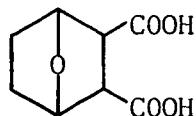


(5-12)

it can be made by a Diels-Alder reaction between cyclopentadiene and maleic anhydride.⁴⁵ Chloromaleic anhydride has also been used to make the corresponding chlorocompound.⁴⁶ The diallyl ester has been reported by Morris, Snider, and Horowitz⁴⁷ for use in polymers and a copolymer of the diallyl ester, ethylene glycol, maleic anhydride, and phthalic anhydride has been reported by Agnew.⁴⁸

Compound (5-12) has been polymerized with dialcohols such as 2-ethyl-1,3-hexanediol to form a polyester that is suitable as a plasticizer for urea and melamine-formaldehyde resins.⁴⁹ By mixing the polyesters obtained from (5-12) and ethylene glycol, triethylene glycol, propylene glycol, or dipropylene glycol with a drying oil, a wrinkle finish coating was obtained.⁵⁰ Another copolymer system was also suggested for coatings or plasticizers depending on composition.⁵¹ The diallyl ester of (5-12) and similar compounds has been prepared and used to make polyesters for surface coatings with good electrical insulating properties.^{52a} Fatty oils and vinyl monomers have been included in a polymer composition using allyl derivatives.^{52b}

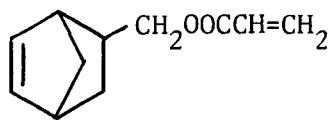
When furan was substituted for cyclopentadiene, a heterocyclic monomer resulted.⁵²



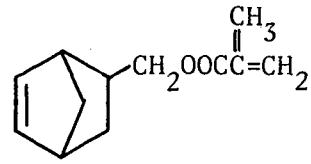
Polymerization occurs with peroxide or metal soaps between 35 and 160°.

Partial polymerization produced a product which could be shaped or molded and which was infusible on further heating.^{53b}

Bicyclo[2.2.1]hept-5-en-2-carboxylic acid has been homopolymerized, and copolymerized with maleic anhydride.⁵⁴ The related bicyclo[2.2.1]-hept-2-en-5-ylmethyl acrylate (5-13) and methacrylate (5-14) have also



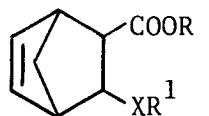
(5-13)



(5-14)

been prepared.⁵⁵ Useful polymers and coatings can result from polymerization of these monomers. A copolymer made from norborneol methacrylate and methyl methacrylate has also been reported.^{55a} A Diels-Alder adduct of cyclopentadiene and allyl alcohol has been polymerized with methacrylic acid.^{56b}

Norbornene and tricycloheptene ether-esters have also been prepared for use in polymers.⁵⁷



R = alkyl (C₁-C₅)

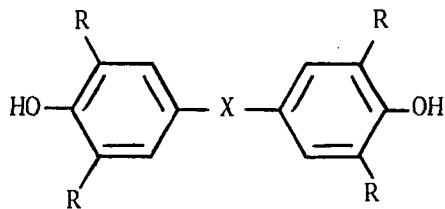
R¹ = alkyl or haloalkyl

X = S, O

These compounds also have fungistat and preemergent herbicidal activity.

Polyesters made from 2,5-diketo-1,4-cyclohexane-1,4-dicarboxylic acid, and methylene bridged derivatives of this acid have been investigated to determine the effect of carboxyl orientation on melting point.⁵⁸ Contrary to earlier belief, it was concluded that aromatic rings and a carbonyl attached to the ring is not necessary for fiber formation. The symmetry of the polymer unit is important, however,

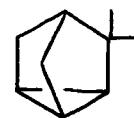
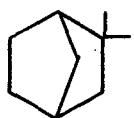
A series of three-dimensional polycyclic bisphenol polycarbonates and polyesters has been patented by Caldwell and Jackson.⁵⁹ The bisphenols disclosed in this patent were of the type:



R = H, halogen, alkyl

X = bicyclic group

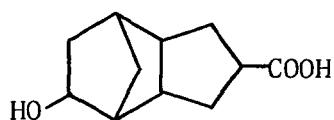
Bicyclic groups included the following:



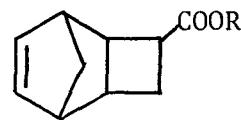
Improved temperature properties and solubility in volatile solvents was claimed for these compounds. Phosphorous was incorporated into the compounds in order to add fire retardant properties.⁶⁰

Flame retardant properties have also been incorporated into the monomers by using hexachlorocyclopentadiene to prepare the bicyclic compound. For example, the Diels-Alder adduct of maleic anhydride and hexachlorocyclopentadiene has been incorporated into fiberglass compositions to impart flame resistance.⁶¹ A small amount of antimony oxide has also been added.

Two somewhat more complicated molecules have also been incorporated into polyesters. These are (5-15)⁶² and (5-16).⁶³



(5-15)



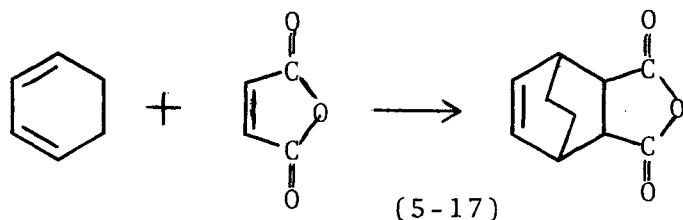
(5-16)

A polymer of (5-16) and styrene was sprayed on wood to form a finish that was free from tackiness after 30 minutes and could be polished after 15 hours.

1-Azabicyclo[2.2.1]heptane, along with several other bicyclic and non-bicyclic heterocyclic amines, has been incorporated into polyester compositions.⁶⁴ The products were used to form films and fibers.

Bicyclo[2.2.2]octanes

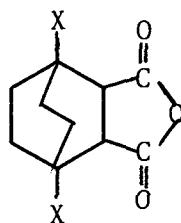
Diels-Alder adducts of cyclohexadiene and maleic anhydride have been used to make polyesters.



For example, compound (5-17) has been condensed with glycerol or pentaerythritol to form polyesters which soften in the 66 to 103° range.⁶⁵

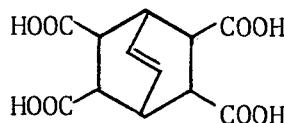
Alkyd resins were prepared by adding linseed oil, sunflower oil, or coconut oil.⁶⁶ These resins formed strong, heat and water resistant coatings.

By using a 1,4-disubstituted diene, bridgehead substituted versions of (5-17) have been made.⁶⁸



X = COOH, COCl, COOR

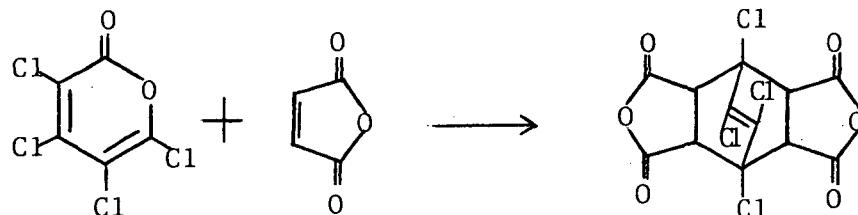
Bicyclo[2.2.2]oct-7-en-2,3,5,6-tetracarboxylic acid and the corresponding anhydride (5-18) has also been used in polymers.



(5-18)

Varnishes⁶⁸ and stoving enamels⁶⁹ have been prepared using this monomer in various formulations. Drying oils have also been prepared from this compound.⁷⁰

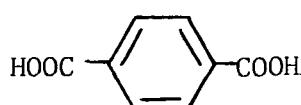
Perchlorocoumalin and maleic anhydride have been condensed to form compound (5-19).



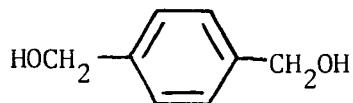
(5-19)

This monomer, which is obviously related to (5-18) has been used to make fire retardant polymers.⁷¹

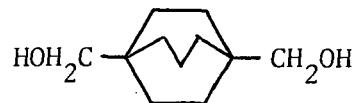
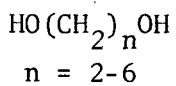
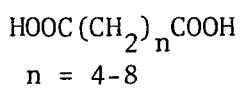
Taimr and Smith⁷² studied a series of polyesters made from various combinations of the following compounds:



(5-20)



(5-21)



Watson⁷³ had previously patented polymers made from (5-20) and (5-21).

Tables of melting point, thermal stability, and oxidation stability were included in the papers for the various compounds studied. In general, replacing a non-bicyclic ring structure with a bicyclo[2.2.2]octane structure had little effect on the melting point of the polymer. A notable exception was observed with polyesters made from open chain glycols and either terephthalic or 1,4-dicarboxybicyclo[2.2.2]octane. In this case, no effect was observed when the glycol contained an even

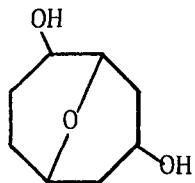
number of methylene groups, but the bicyclo derivative had a significantly lower melting point when the glycol had an odd number of methylene groups. A similar type of behavior had been reported earlier with polyesters obtained from p-xylylene glycol.⁷⁴

When the bicyclo[3.2.2]nonane ring system was used in place of the bicyclo[2.2.2]octane ring system, the melting point was significantly reduced. This phenomenon was attributed to the observation that the functional groups on the bridgehead carbons are located at an angle of about 150° in the bicyclo[3.2.2]nonane system compared to 180° in the bicyclo[2.2.2]octane system. The bond angle should reduce symmetry in the crystal and therefore lower the melting point. When both the alcohol and the acid groups were bicyclic, a significant increase in melting point was observed.

Thermal stability showed a similar pattern. With one ring present in the polymer (bicyclic or not) the molecule was less stable than when two rings (one bicyclic) were present. Maximum thermal stability was observed with two bicyclic rings in the unit cell. Oxidative stability was also greatly increased by the presence of two bicyclo[2.2.2]octane rings in the molecule.

Batzer and Benzing⁷⁵ used 2,5-dihydroxy-1,4-dicarboxybicyclo[2.2.2]-octane as a monomer with hexane-1,6-diol as a model for cellulose. The corresponding compound from 2,5-diketo-1,4-dicarboxybicyclo[2.2.2]octane was also prepared. The influence of hydrogen bonding on solubility, softening point, crystallization, and solution behavior was discussed.

Oxidation resistant polymers have been reported from 2,6-dihydroxy-9-oxabicyclo[3.3.1]nonane and derivatives.⁷⁶



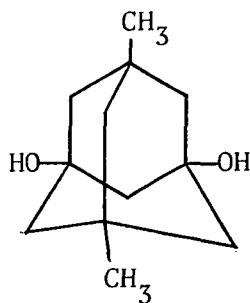
Both polyesters and polyurethanes have been prepared from this monomer and the appropriate diacid or diisocyanate.

Polyester resins have also been made from acetylenic diesters and polyols.⁷⁷ An olefinic linear polyester is obtained by addition of a diol of the type HXYXH across the triple bond. In this case, X is oxygen or sulfur and Y is an alkyl or haloalkyl group containing 2-18 carbon atoms or a polyglycol containing up to 100 oxygen atoms. The polymers were cast into films, spun into fibers, and used as coatings and for impregnation. Compression molding produced tough, transparent objects.

Adamantanes

The adamantane ring structure has been incorporated into polyesters by addition of both carboxylic acid and hydroxyl groups to the ring. Dimethyl adamantane 1,3-dicarboxylate has been used to make heat resistant fibers and films.⁷⁸

1,3-Dihydroxy-5,7-dimethyladamantane has been polymerized with

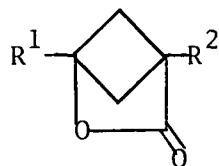


maleic anhydride,^{79b} phthalic anhydride,^{79b} or diethyl malonate.^{79a} These polyesters are reported to have good light, hydrolysis and thermal stability. Films and fibers have been prepared from these compounds.

Acrylic and methacrylic esters of 3,5-dimethyl-1-adamantanol have been prepared.⁸⁰ Polymers have been prepared from these monomers.

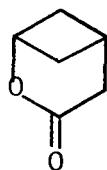
Bicyclic lactones

As with the bicyclic lactams, the bicyclic lactones have been prepared and polymerized. The resulting polymers are not bicyclic. For example, 2-oxabicyclo[2.1.1]hexane-3-ones have been polymerized.

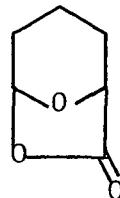


A white polymer which could be pressed into clear, self-supporting film at 100° resulted.

Polymers have also been prepared from 3-oxabicyclo[3.1.1]heptan-2-one (5-22)⁸² and 3,8-dioxabicyclo[3.2.1]octan-2-one (5-23).^{83a}



(5-22)



(5-23)

Compound (5-23) produces thermosetting polymers that are useful as protective coatings. 3-Oxabicyclo[2.2.2]octan-2-one derivatives have also been prepared.^{83b} There is no evidence, outside of the work of Hall,⁸⁴ that any attempt was made to convert them to polymers.

Miscellaneous Polyesters

Esters and polyesters have been reported from 8-hydroxytricyclo-4-decene.⁸⁴ High melting resins are reported. A polymer prepared from tricyclodecanedicarboxylic acid and glycerol was a glassy material which hardened to a rubber-like infusible mass on heating.⁸⁵

Cagelike polymers have been prepared by adsorption of polymers on cellulose.⁸⁶ Washfastness was improved with these materials. Mixed carboxylic acid esters of cellulose in which bicyclic acids are incorporated have been used as antistatic and antihalation layers and as modifiers for coupling components for color photography.⁸⁷

Diazabicyclooctane was used, among other acids and amines, in a study on the inversion of maleic acid end groups on polyesters into fumaric acid.⁸⁸ Diazabicyclooctane has also been treated with sulfur dioxide to make an additive for ethylenically unsaturated polyesters.⁸⁹ The adducts were also useful as catalysts for polyurethane formation.

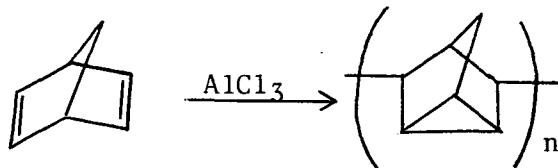
Halogenated bicyclic aromatic hydrocarbons have been used to treat polyesters.⁹⁰ Improved dyeability and dimensional stability resulted.

Polyolefins

Polyolefins using bicyclic and cage ring systems have not been used extensively. Polybicycloheptanes and polyadamantanes have probably been the most thoroughly studied. Thermal and oxidative stability generally result from the addition of bicyclic and cage groups to the polyolefin chain.

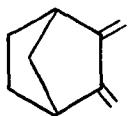
Bicyclo[2.2.1]heptanes

Cationic polymerization of norbornadiene has been reported by Kennedy and Hinlicky.⁹¹ Polymerization using aluminum chloride was accomplished at several temperatures between 40° and -123°. Only the material produced at -123° was completely soluble. Other temperatures produced a crosslinked material. This observation is consistent with an earlier patent⁹² in which poly-bicyclo[2.2.1]-2-heptene was claimed and which was reported to not melt below 300°. The repeating unit in the soluble material is apparently a 2,6-disubstituted nortricyclene.

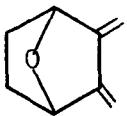


3-Allylnortricyclene has also been prepared and polymerized.

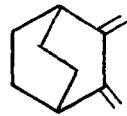
The following bicyclic monomers have all been polymerized by Borne, Miller, Rose and Wood.⁹⁴



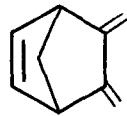
(5-24)



(5-25)



(5-26)

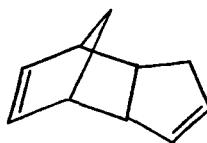


(5-27)

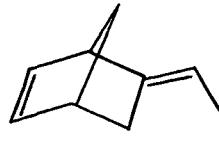
Polymers of compounds (5-24), (5-25), and (5-26) are all soluble in organic solvents. They could be molded and drawn, and showed crystalline x-ray patterns. Compound (5-27) was insoluble in organic solvents, and decomposed without melting.

In a study of the mechanism of polymerizations, Farmer and Martin⁹⁵ observed that dimerization of $\beta\gamma$ -dimethylbutadiene gives methylenotetramethylbicycloheptane. The exact structure of the product was not determined, and two alternatives were proposed.

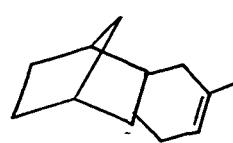
Copolymerization of ethylene with dicyclopentadiene (5-28), ethylidenenorbornene (5-29), and methyl endomethylene hexahydronaphthalene (5-30)



(5-28)



(5-29)

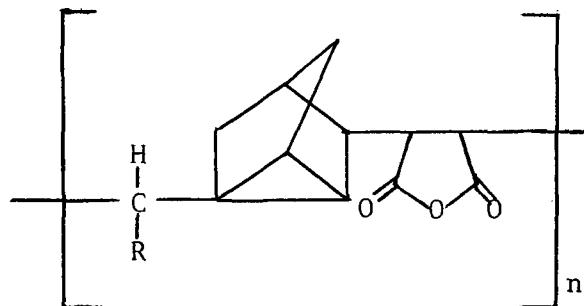


(5-30)

has been reported by Schnecko, Caspary and Degler⁹⁶ using a Ziegler-Natta catalyst. Physical properties of the polymer varied with composition. Above 15-20% diene, the material is amorphous.

Cross-linked copolymers of ethylene and derivatives of bicyclo[2.2.1]hept-2-ene have been reported.⁹⁷ Protective coatings, extruded articles, and films have been made from these materials.

Pliimer and Keller⁹⁸ have studied copolymers of bicyclo[2.2.1]hept-2-ene with vinyl acetate and vinyl chloride. Pledger and Butler have similarly prepared a copolymer⁹⁹ between bicyclic dienes and maleic anhydride. Polymers such as



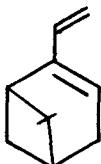
were prepared and characterized.

Polymerization of 7-oxabicyclo[2.2.1]heptane has been accomplished using phosphorous pentafluoride in methylene chloride.¹⁰⁰ The rate of polymerization was studied, and an activation energy of 15.4 kcal/mole was reported.

Cyclopentadiene has been polymerized and copolymerized to form useful polymers.¹⁰¹ The products are presumably at least partially bicyclic. Di and tricyclopentadiene, obtained by catalytically polymerizing cyclopentadiene, has been successfully polymerized with maleic anhydride.^{101b}

Bicyclo[3.1.1]heptanes

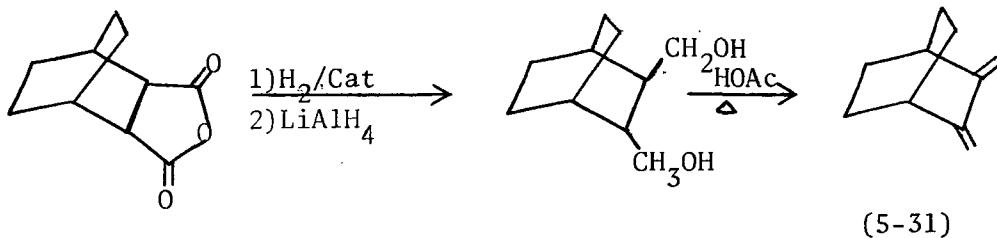
6,6,Dimethyl-2-vinyl-bicyclo[3.1.1]hept-2-ene (trivial name-nopadiene) polymerizes slowly to a sticky yellow solid in the presence



of benzoyl peroxide.¹⁰² It also slowly copolymerized with butadiene. Nopene forms high molecular weight polymers (MW 8000-12000) by thermolysis of benzoyl peroxide.¹⁰³ The product is similar to polystyrene but the softening point is higher.

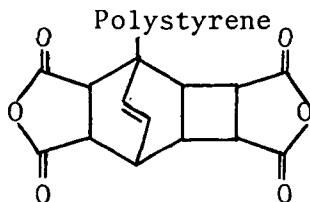
Bicyclo[2.2.2]octanes

The Diels-Alder adduct of cyclohexadiene and maleic anhydride has been converted to compound (5-31).¹⁰⁴ This compound formed a



crystallin polymer using potassium persulfate-n-dodecylmercaptan as a catalyst. The polymer had a Vicat softening point of 85°.

The following compound has been incorporated into polystyrene.¹⁰⁵

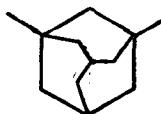


Between 0.1 and 10% are recommended.

A copolymer between 1,3-butadiene and 2-methyl-5-vinylpyridine has also been reported.¹⁰⁶

Adamantanes

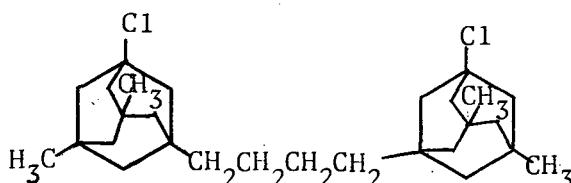
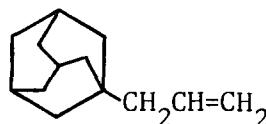
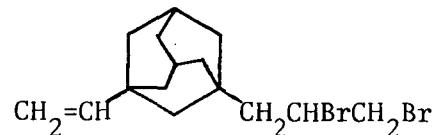
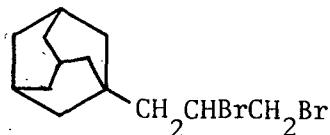
Polyadamantane has been prepared by Reinhardt.¹⁰⁷ The adamantane nuclei are connected at the 1 and 3 positions.



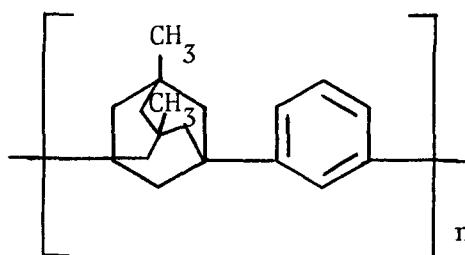
The polymer does not melt below 420° and is greater than 80% crystallin.

It is also insoluble in boiling acid, alkali, and common organic solvents.^{107a} Derivatives have also been made which are useful in preparing other types of polymers. For example, monomers of the type RAX_mAR^1 have been prepared, where A is adamantane, X is a divalent radical, and R and R^1 are H or monovalent radicals, and m is 0 or 1.

Polymers containing adamantane nuclei joined by short polymethylene chains have also been prepared.¹⁰⁸ Monomers such as the following have been used.



Thermally stable polymers are claimed to result.^{108a} A similar polymer has been made by treating 1,3-dimethyladamantane with *p*-di-*tert*-butylbenzene in the presence of aluminum chloride.¹⁰⁹ The resulting polymer formed films and coatings having a high degree of thermal and oxidative stability.

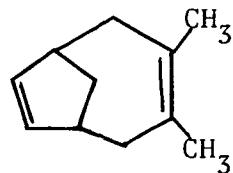
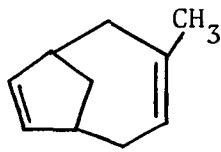


Similarly, allyladamantane has been polymerized using a modified Ziegler-Natta catalyst system.^{109b}

Miscellaneous Polyolefins

Bicyclo[2.2.1]heptadiene and allene have been converted to exo-3-methyltricyclo[4.2.1.0^{2,5}]nona-3,7-diene using palladium or nickel as a catalyst.¹¹⁰ The material is reported to form novel polymers.

Copolymerization of ethylene, propylene, and 3-methylbicyclo[4.2.1]nonan-3,7-diene, or 3,4 dimethylbicyclo[4.2.1]nona-3,7-diene



¹¹¹
has been carried out. Vulcanizable, linear, amorphous olefin copolymers of high molecular weight resulted.

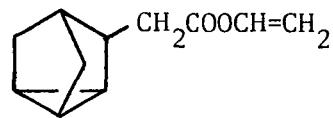
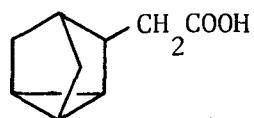
Polyvinyls

Although not many examples exist, bicyclic and cage compounds may be incorporated into several vinyl polymer systems. For example, bicyclo[2.2.1]hept-2,5-diene has been copolymerized with vinyl chloride. When a graft terpolymer was prepared with several other polymers, improved shock resistance without lowered deflection temperature was observed.¹¹²

The bicyclic portion of the polymer presumably had a nortricyclene ring structure. An adduct of α -terpinene and maleic anhydride has also been incorporated into a vinyl chloride polymer.¹¹³ The product is colorless and has good adhesive power. The addition of camphor,

fenchone, α -isocamphenilone, apocamphor, norcamphor, or 4,4-dimethylbicyclo[3.2.1]octan-2-one has also been reported to improve various properties of vinyl chloride resins.¹¹⁴

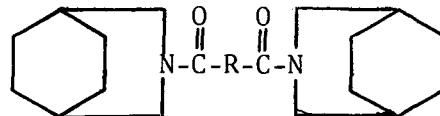
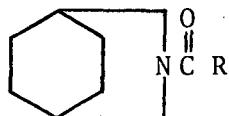
3-Nortricyclylacetic acid and vinyl 3-nortricyclylacetates have been polymerized to form a clear solid.¹¹⁵ Camphene and 5-methylbicyclo-



[2.2.1]hept-2-ene have been polymerized using a Ziegler-type catalyst, but 5-methylbicyclo[2.2.2]oct-2-ene failed to react.¹¹⁶

Triethylenediamine has been incorporated into a polyvinyl alcohol based adhesive to impart quick tack properties.¹¹⁷ Triethylenediamine has also been incorporated into a divinyl sulfone plastic foam.¹¹⁸

N-Acyl derivatives of 3-azabicyclo[3.2.2]nonane have been suggested as comonomers for vinyl polymers. It was further suggested that these



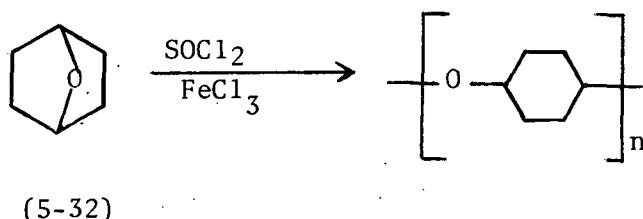
R = alkyl

polymers should show good heat stability and have a good affinity for dyes.¹¹⁹ These compounds also have fungicidal properties.

Vinyladamantanes have also been reported.¹²⁰ Their use in polymers was not suggested, however.

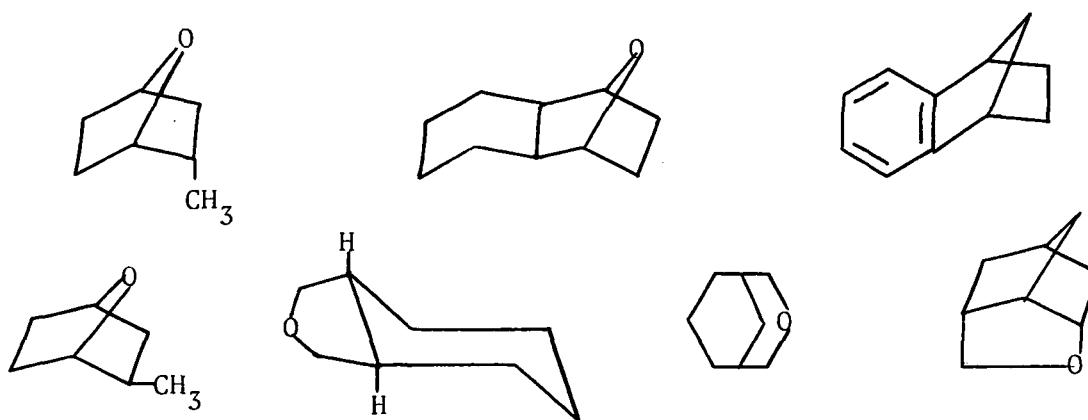
Polyethers and epoxyresins

Bicyclic and cage compounds have not been used extensively in polyether or epoxyresins. Of those that have been used, 7-oxabicyclo[2.2.1]-heptane (1,4 epoxycyclohexane) (5-32) seems to be the most common. Wittbecker, Hall, and Campbell¹²¹ have studied this system fairly thoroughly. Lewis Acid catalysts were employed to produce the polymer, which is not bicyclic. The polymer was found to be a high melting



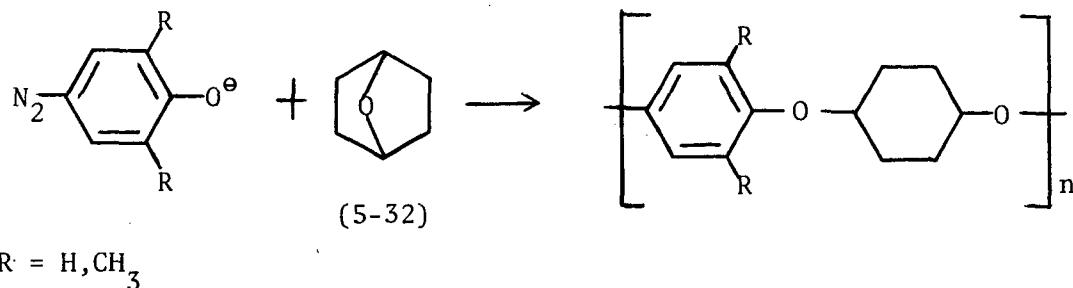
(5-32)

white solid that was insoluble in most solvents except phenols. This observation is in general agreement with the observations of Wilkins.¹²² Lower melting polymers were obtained from endo and exo-2-methyl-7-oxabicyclo[2.2.1]heptane. These authors also studied the following compounds related to (5-32).

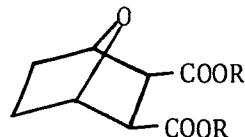


Pizzirani and Giusti¹²³ have also polymerized (5-32). They found that the polymer degraded rapidly in light to form 1,4-dichloro-cyclohexane. The kinetics of the polymerization¹²⁴ and the relative rate¹²⁵ compared to other polymers has also been studied.

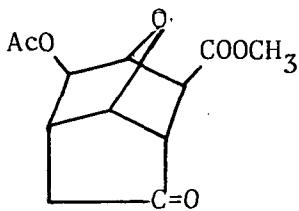
Copolymers of (5-32) and other materials have been prepared by several authors. Copolymers with tetrahydrofuran,^{121,122,126} trioxane,¹²⁷ and other cyclic ethers¹²⁸ seem to be most common. Compound (5-32) is one of several cyclic ethers that was copolymerized with p-benzoquinone diazide.¹²⁹ Some related monomers that have been studied are 7-oxa-



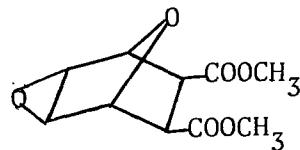
bicyclo[2.2.1]heptan-2,3-dicarboxylic acid,¹³⁰ its anhydride¹³¹ and esters.¹³²



Compounds (5-33) and (5-34) have also been used in polyethers,¹³³ as



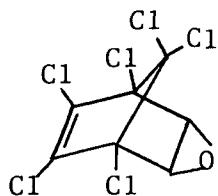
(5-33)



(5-34)

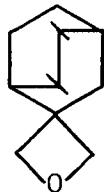
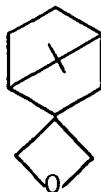
has 2-exo-chloro-7-oxabicyclo[2.2.1]heptane.¹³⁴ The chlorinated equivalent of (5-32) has also been used to make polyethers.¹³⁵

Epoxy-polychloro-bicyclo[2.2.1]heptene has been prepared and poly-



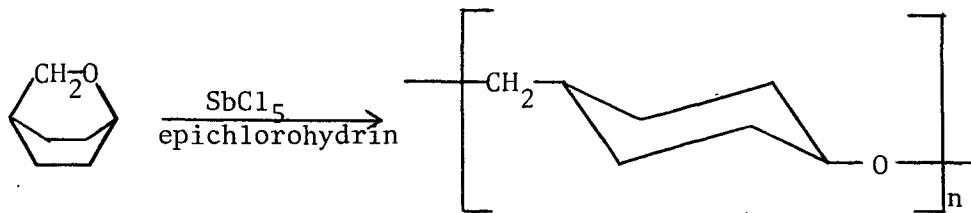
merized by Kleiman.¹³⁶ The resins have unusual heat and fire resistant properties. Polyesters have also been prepared from the corresponding glycol that have fire resistant, fungistatic, and heat resistant properties. The compound by itself also has insecticidal and fungicidal properties. The biological properties are enhanced by treating the compound with mercuric chloride or other heavy metal salts.

Polymers have also been made from spirooxetanes¹³⁷ of the type



These compounds have also been used in polyethers. The products have high melting points, are crystallin, and are useful for molding.

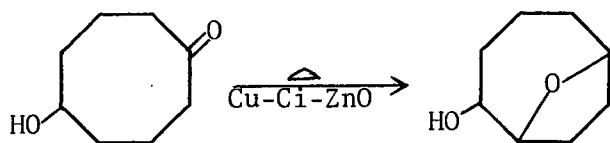
Polymerization of 2-oxabicyclo[2.2.2]octane was reported by Saegusa, Hodaka, and Fujii.¹³⁸



The products were sticky solids that were soluble in methylene chloride.

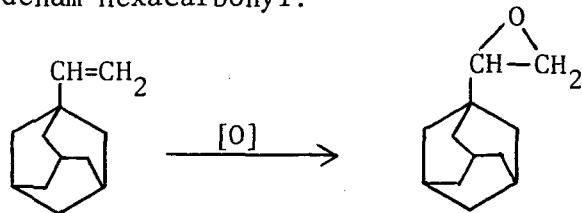
Ring opening polymerization of 4-methyl-2,6,7-trioxabicyclo[2.2.2]-octane, 6,8-dioxabicyclo[3.2.1]octane, and 3,6,8-trioxabicyclo[3.2.1]-octane has been achieved by Steuck¹³⁹ with the aid of appropriate Lewis acids. Okada, Sumitomo, and Hibino¹⁴⁰ have also investigated the polymerization of 6,8-dioxabicyclo[3.2.1]octane using boron trifluoride etherate as the initiator.

A polymer of 2-hydroxy-9-oxabicyclo[4.2.1]octane has been prepared

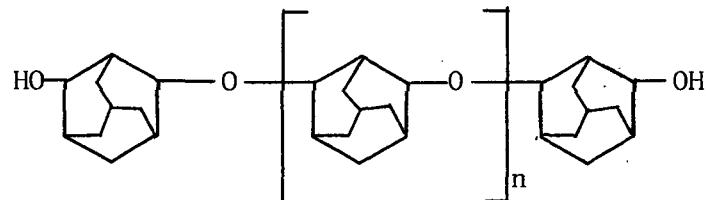


from cyclooctane-1-ol-5-one. The monomer is useful in pharmaceuticals, and the polymer is useful for synthetic fibers.¹⁴¹

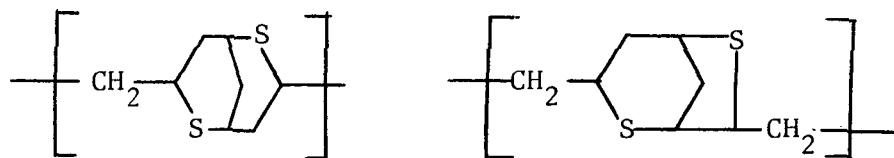
Vinyladamantane¹⁴² has been converted to the epoxide with t-butyl-peroxide and molybdenum hexacarbonyl.¹⁴³



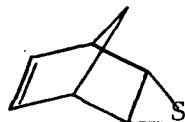
Polymers made from the epoxide are useful as wax additives, gaskets, and rubberlike materials. A polyether has been made with adamantyl groups.¹⁴⁴



Polythioethers have also been prepared. For example, divinyl sulfide has been polymerized under free radical conditions.¹⁴⁵ The following bicyclic structures are among the products.



Bicyclic resins derived from thiiranes have also been reported by Lautenschlager and Schnecko.¹⁴⁶



An anionic or cationic catalyst system was used so that the episulfide group would polymerize with the olefinic group. Other monocyclic materials were also discussed. A molding compound has been prepared from a mixture of poly(ethylene episulfide) and N,N^1 -di-tert-butylhexamethylenebis(carbodiimide).¹⁴⁷

Polyurethanes

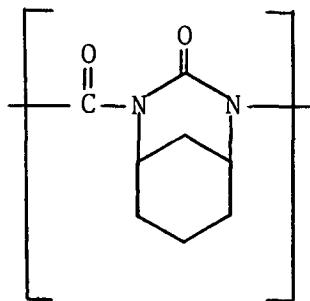
Except for triethylenediamine (1,4-diazabicyclo[2.2.2]octane) and selected derivatives, bicyclic and cage compounds have not been used extensively in polyurethanes. Triethylenediamine has been used primarily as a catalyst in the formation of polyurethane foams. Part I of the bibliography for Chapter 5 contains a listing of the papers and patents in this area. Part II of the bibliography is a similar listing of papers and patents where the abstracts were not specific about the bicyclic material involved. We did not obtain copies of the original papers for the listings in parts I or II of the bibliography.

While triethylenediamine is the most common bicyclic catalyst, others have been used. For example, 5,9-dimethyl-1-azabicyclo[3.3.1]nonane and 5,9-dimethyl-1-azabicyclo[3.3.1]nonene have both been reported to be urethane catalysts.¹⁴⁸ Tertiary amines derived from 3-azabicyclo-[3.2.2]-

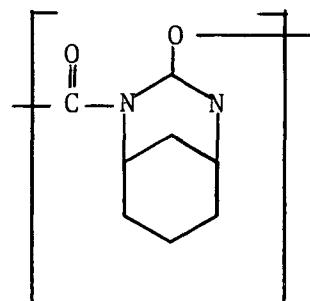
nonane have also been reported to catalyst for the formation of polyurethanes.

A few examples also exist in which the bicyclic material is part of the polyurethane. For example, 7-oxabicyclo[2.2.1]hept-2-ene-5-sulfonyl isocyanate and 1,2,3,4,7,7-hexachlorobicyclo[2.2.1]hept-2-ene-5-sulfonyl isocyanate have been prepared.¹⁵⁰

N-2-Quinuclidiyurethane has been polymerized with itself¹⁵¹ by two routes. cis-1,3-Di(isocyanate)cyclohexane has been polymerized¹⁵² to form a polymer with the structural units (5-35) and (5-36) in a ratio of 65:35.



(5-35)



(5-36)

A tricyclic siloxane has been incorporated into polyurethane binders in order to moderate ballistic properties of a propellant.¹⁵³ The siloxane was 1,3,5,7,9,11-hexaphenyl-5,11-dihydroxytricyclo[7.3.1]^{3,7}hexasiloxane (Dow Corning Z-6018). The siloxane increased the burning rate of polyurethane propellant by 188%.

Elastomers

Bicyclic and cage compounds have been used as the main part of the polymer chain and as accelerators in rubber compositions. In addition,

olefins such as norbornene and dicyclopentadiene have been mixed with phenol-formaldehyde resins and other components to form an adhesive for tire cords.¹⁵⁴

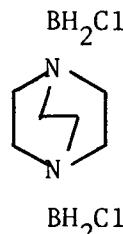
Dicyclopentadiene has been found to be a useful component in vulcanizable olefin multipolymers.¹⁵⁵ The major components are ethylene, propylene, or 1-butene. Tetracyclopentenyl has also been copolymerized with ethylene and an α -olefin to form an elastomeric terpolymer.¹⁵⁶

Vanadium containing Ziegler catalysts have been employed to form vulcanizable olefin copolymers containing 7-methylenebicyclo[2.2.1]hept-2-ene, 7-isopropylidenebicyclo[2.2.1]hept-2-ene, bicyclo[2.2.2]octa-2,5,7-triene, or 8-methylbicyclo[3.2.2]nona-2,6-diene. Ethylene and α -olefins are also part of these polymers.¹⁵⁷ Similarly, ethylene and propylene have been copolymerized with either 3-methylbicyclo[4.2.1]nona-3,7-diene or 3,4-dimethylbicyclo[4.2.1]nona-3,7-diene.¹⁵⁸

Bicyclo[2.2.1]-5-heptene-2,3-dicarboxylic acid, its anhydride; monomethyl esters, and various salts has been used to control vulcanization of a rubber compound containing sulfur and an organic accelerator.¹⁵⁹ This same acid has also been used for the vulcanization of rubber.¹⁶⁰ This was accomplished by heating a 1-10% mixture of the compound in the rubber to 75-150°. At this temperature, a reverse Diels-Alder reaction takes place forming maleic anhydride which vulcanizes the rubber.

A plasticizer for elastomers has been prepared from furfuryl acetate and maleic anhydride.¹⁶¹ The compound is 3-acetoxymethylene-3,6-endoxohexahydrophthalic anhydride or its butyl ester.

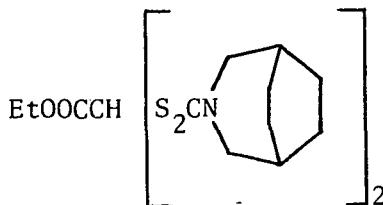
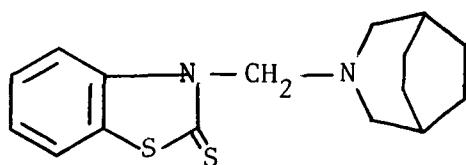
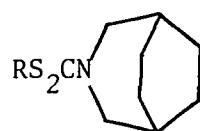
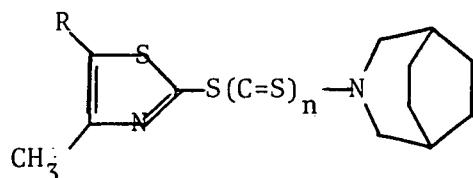
Vulcanization of natural rubber has been accomplished using tri-
ethylenediaminebischloroborane.¹⁶²



Good reversion and age resistance were observed using this material.

1,1,4,7,10,10-Hexamethyltriethylenetetramine and triethylenediamine have also been used as vulcanizing agents.¹⁶³

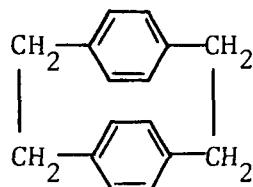
A series of amines derived from 3-azabicyclo[3.2.2]nonane have been used as accelerators and curing agents for rubbers.¹⁶⁴ Some typical compounds are



Natural rubber tread stock and styrenebutadiene rubber have been cured with these materials.

Poly-p-xylylenes

The di-p-xylylenes (5-37) are a somewhat different type of cage

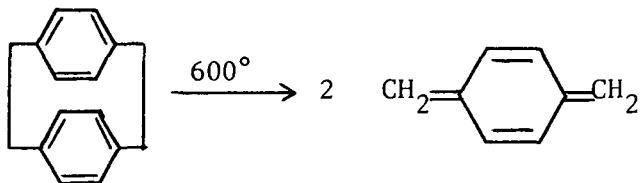


(5-37)

compound than those in most of this report. The unique properties of polymers prepared from these monomers, however, makes them valuable materials for special applications.

The polymer

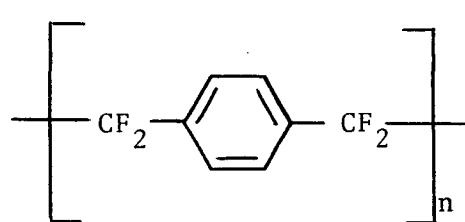
The actual monomer, p-xylylene, is generated quantitatively by vacuum vapor phase pyrolysis of di-p-xylylene at 600°.



The polymer is then formed quantitatively by spontaneous polymerization on a surface maintained below 30°. The resulting polymer is linear,

high molecular weight, and soluble in chlorinated biphenyls.¹⁶⁵

In addition to the parent di-p-xylylene, monomers with a variety of substituents have been prepared and polymerized. A polymer containing fluorine groups in place of the hydrogen atoms on the methylene groups is of particular interest.¹⁶⁶



This polymer exhibits "remarkable" thermal and oxidative stability at elevated temperatures. Useful mechanical and electrical properties are retained even after aging for 3000 hours at 250° in air.

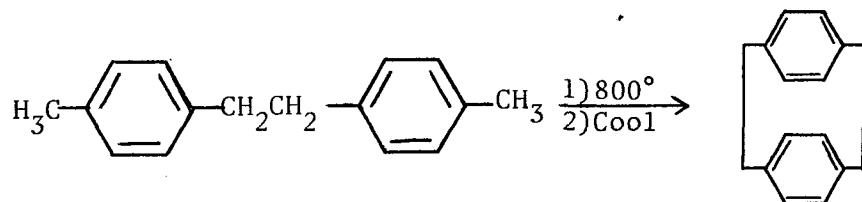
A mass spectral study of poly-p-xylylenes has been conducted.¹⁶⁷ Another study of charge storage on polymer foils was conducted using poly-p-xylylene along with commercial polymer films.¹⁶⁸ Copolymers were obtained by pyrolysis of mixtures of substituted p-xylylenes.¹⁶⁹

From a commercial standpoint, poly-p-xylylene is a good electrical insulator and may be deposited in a thin film. The Union Carbide Corporation has attempted to commercialize the polymer¹⁷⁰ under the trade name "Parylene". Both the parent p-xylylene (Parylene N) and the monochlorinated derivative (Parylene C) have been made available. Union Carbide claims that the polymers have good thermal stability in the absence of air (such as hermetically sealed units and with coated parts potted with phenolic molding compounds).

In addition to dielectric properties, the parylenes are reported to have superior toughness at cryogenic temperatures. Parylene C is also an excellent barrier for the permanent gases and water vapor.

The Monomer

The di-p-xylylene used as the monomer precursor has been generated by several procedures. For example, pyrolysis of 1,2-di-p-tolylethane at 800-1000° followed by quenching in an inert organic solvent at a temperature below 300° has been reported.¹⁷¹



Pyrolysis of p-xylene mixed with steam at 850-900° has also been reported to form di-p-xylylene in 8-10% yield.¹⁷² Direct polymerization and copolymerization with maleic anhydride and 2-chloro-1,3-butadiene were also obtained by pyrolysis of p-xylene¹⁷³ at 795-920°.

An iron based alloy containing chromium and nickel has been used to catalyze the formation of p-xylylene from oxygen and a p-xylylene precursor.¹⁷⁴ Presumably any of the above precursors could be used.

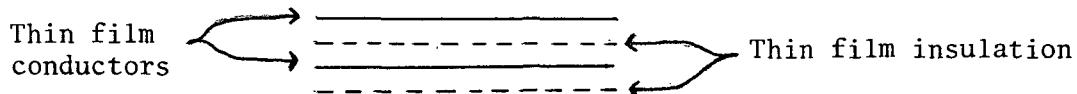
A mixture of di-p-xylylene and terephthalic acid was obtained when p-xylene was pyrolyzed in a carbon dioxide atmosphere.¹⁷⁵ Thus a contact time of 5.9×10^{-3} sec. in a quartz tube heated to 1020° followed by quenching at -78° in hexane was used to produce 3.56% di-p-xylylene and 2.2% terephthalic acid.

Substituted di-p-xylylenes have also been patented. For example, alkyl¹⁷⁶ and cyano¹⁷⁷ substituents have been specifically patented.

Specific Applications

The unique ability of p-xylylene to form thin films has led to several specific applications of these polymers. One of the most significant applications is in thin film capacitors.¹⁷⁸ These capacitors are made by depositing a 10 nm film of poly-p-xylylene as an insulator on one side of one of the two metal plates. A wide useful temperature range and a high dielectric strength are possible for this technique.

The logical next step in the process of miniaturization would be to deposit a thin film of poly-p-xylylene followed by a film of metal, another layer of insulation, another layer of conductor, and finally a layer of insulation.



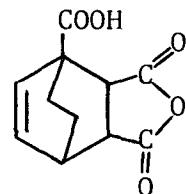
Using this technique, it should be possible to make extremely small capacitors with a high capacitance. Apparently no attempt to do this has been reported.

An electric insulation paper has been made by treating kraft paper with p-xylylene vapors.¹⁷⁹ A 2 weight per cent polymer deposition gave an insulating paper with a 9920 V/mm breakthrough voltage and a 5.57 kg/mm tensil strength.

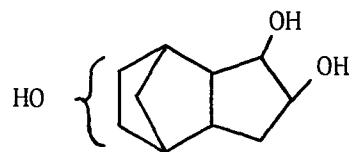
Particulates have been encapsulated by exposure to p-xylylene vapors.¹⁸⁰ A variety of materials have been encapsulated by this technique such as lithium, lithium aluminum hydride, molecular sieves, ammonium perchlorate, rubber stoppers, and aluminum films. As a test of this technique, two pellets of encapsulated lithium were placed in water for 30 days with no noticeable hydrogen evolution.

Miscellaneous Polymers

Several bicyclic polymers have been reported that do not fit the general topics already discussed. For example, crosslinking of polymers has been achieved with bicyclo[2.2.2]oct-5-ene-1,2,3-tricarboxylic acid anhydride¹⁸¹

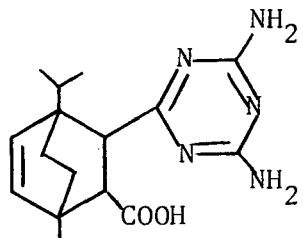


and tricyclodecane-(5,2,1,0^{2,6})triool-(3,4(8-9)).¹⁸²



Cation exchange resins have been made by treating 7-oxabicyclo-[2.2.1]heptan-2,3-dicarboxylic acid with formaldehyde.¹⁸³

Alicyclic guanamines have also been prepared for use in resins by reaction with formaldehyde.¹⁸⁴



Polymer Additives

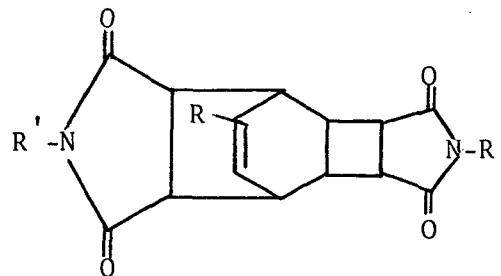
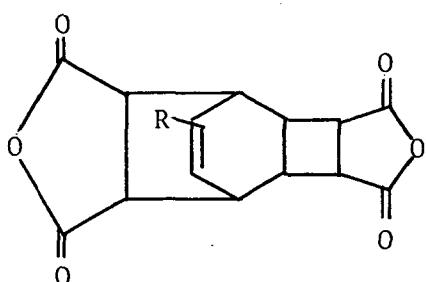
Almost all polymers need additives of one type or another to aid in curing or to impart desirable properties to the polymer. Bicyclic compounds have been used in several types of additives, such as curing agents, plasticizers, stabilizers, and flame retardants.

Curing Agents

Probably the most extensively used bicyclic curing agent is 1,4-diazabicyclo[2.2.1]octane. This compound and derivatives have been used so extensively that they will not be discussed in detail here. References to the use of these compounds to cure polyesters, polyolefins, epoxides, poly ethers, and miscellaneous other polymers is found in part III of the bibliography for this chapter.

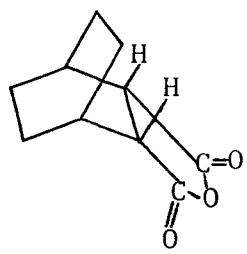
Several bicyclic compounds have been used as curing agents for epoxy resins. For example, terpene hydrocarbons have been incorporated into one curing formulation.¹⁸⁵ Maleic anhydride adducts with benzene

have also been used.¹⁸⁶

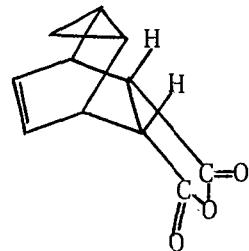


Bicyclic curing agents have been found to be excellent for use as char-forming insulative materials for heat shields for re-entry vehicles.¹⁸⁷

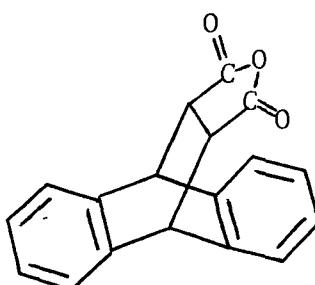
The specific compounds studied were:



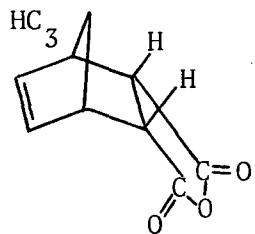
Bicyclo[2.2.2]octa-5-ene-
2,3-dicarboxylic anhydride
(BOCA)



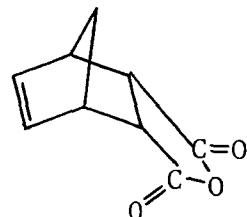
3,6-Endocyclopropylene-
Δ⁴-tetrahydronaphthalic
anhydride (CPTA)



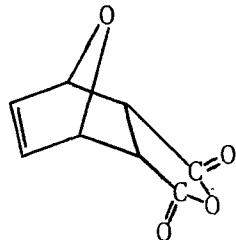
9,10-dihydro-9,10-ethanoanthracene
-11,12-dicarboxylic anhydride (AMAA)



Methylbicyclo[2.2.1]hepta-5-ene-2,3-dicarboxylic anhydride (NMA)



Bicyclo[2.2.1]hepta-5-ene-2,3-dicarboxylic anhydride (NA)



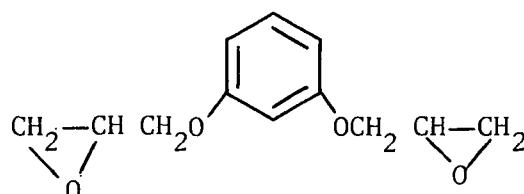
7-oxo-bicyclo[2.2.1]hepta-5-ene-2,3-dicarboxylic anhydride (FMAA)

In addition to being good char formers, these compounds also decompose thermally to form gaseous products that are poor heat conductors.

The retro Diels-Alder reaction, which generally precedes char formation, does not rupture the polymer backbone, thus helping to maintain structural

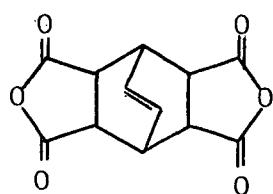
strength. Another feature of the system is that an olefin is produced in the skeleton during the retro Diels-Alder reaction which may serve as a site of possible crosslinking during further heating.

These same systems have also been studied using resorcinol diglycidyl ether.¹⁸⁸

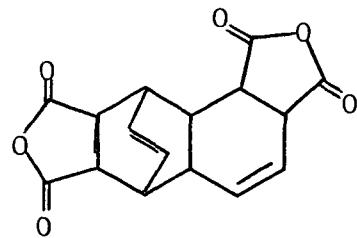


Superior char formation is reported for these materials also.

Two other Diels-Alder adducts that have been used to cure epoxy resins are (5-38)¹⁸⁹ and (5-39).¹⁹⁰



(5-38)



(5-39)

These compounds have also been used in polyester and polyamide formulations.

Amines other than triethylenediamine have been used to cure epoxides. For example, 1,3-diamino-adamantane has been reported as an epoxy curing agent.¹⁹¹ Tricyclodecanediamine has also been reported to produce epoxy resins of outstanding mechanical and chemical properties.¹⁹²

Organic peroxides are commonly used as free radical polymerization initiators, and many compounds, with a varying degree of stability, are commercially available. Only a few bicyclic peroxides have been reported. Some of these materials should be useful as polymerization initiators. For example, bicyclo[2.2.2]octane-1-formyl peroxide is reported to be more stable than pivaloyl peroxide and less stable than isobutyryl peroxide.¹⁹³ The products of thermal decomposition corresponded to a mixture of radical and ion pair or carboxy-inversion products. Only radical products were formed by photolysis.

While Leffler and More¹⁹³ were unable to prepare adamantane peroxide, Boguslavskaya, Etlis, Brovkina, and Razuvayev¹⁹⁴ have used it to initiate polymerization of methyl methacrylate. 1-Adamantylsulfonyl acetyl peroxide has also been used to polymerize vinyl chloride.¹⁹⁵

Plasticizers

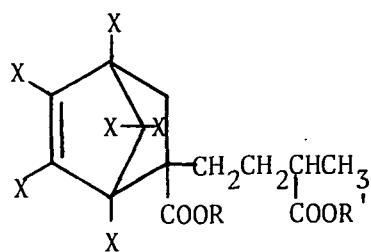
Most commercial polymers contain at least a limited quantity of plasticizer to improve their properties. Some polymers such as the flexible forms of polyvinyl chloride contain large quantities of plasticizer. A wide variety of materials have been used as plasticizers. Butyl and octyl phthalate are probably the best known.

Several bicyclic systems have also been incorporated into polymers as plasticizers. Terpene and camphor derivatives, for example, have been used as plasticizers for poly(trifluorochloroethylene).¹⁹⁶ Difenchyl oxydiacetate, bis(3,3-diethylbicyclo[2.2.2]octan-2-yl)oxydiacetate, and bis(1,3,3-triethylbicyclo[2.2.2]octan-2-yl)tetramethylenedioxydiacetate

have similarly been proposed as plasticizers for polyvinyl chloride, cellulose ethers, and cellulose esters.¹⁹⁷ Selected terpene or sesquiterpene alcohols and their esters have been suggested as plasticizers for vinyl resins, nitrocellulose, and ethylcellulose.¹⁹⁸ For example, nopinenylmethanol acetate was suggested for polyvinyl chloride. The reaction of terpenes with unsaturated dicarboxylic acids followed by esterification of the acid groups produced compounds such as 1-methyl-4-propylbicyclo[2.2.2]oct-5-ene-2,3-dicarboxylic acid which are reported to be plasticizers for plastics and lacquers.¹⁹⁹

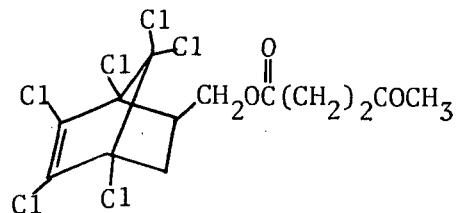
Bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid esters have been used as plasticizers for polyvinyl chloride. Specifically, the dibutyl ester of ethylene glycol bis(bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid) has been reported,^{200a} as has di-2,5-endomethylene- Δ^3 -tetrahydrobenzyl sebacate.^{200b} The Diels-Alder adduct of furfuryl alcohol and maleic acid has been esterified with 2-ethylhexyl alcohol to form a plasticizer for polyvinyl chloride.^{200c}

Chlorinated derivatives of these materials have also been prepared. For example, 1,4,5,6-tetrachloro-7,7-dialkyloxybicyclo[2.2.1]-5-heptene-2,3-dicarboxylic acids have been reported by McBee and Newcomer.²⁰¹ Compound (5-40) has been suggested as a plasticizer for PVC, and alkyd



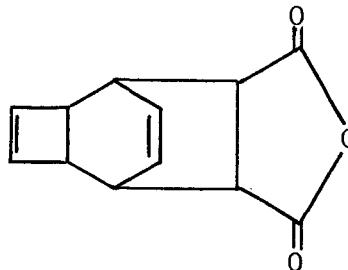
(5-40)

resins as well as pesticides.^{202a} Halogenated bicyclic keto acid esters have also been used to plasticize vinyl resins. Specifically, 1,2,3,4,7,7-hexachloro-2-norbornene-5-ylmethyl levilenate, among other compounds,



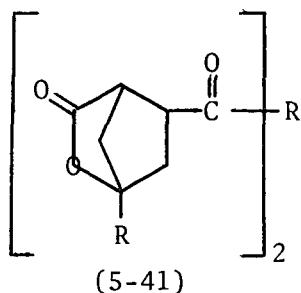
has been utilized.^{202b} Hexachlorocyclopentadiene adducts of unsaturated amides have been suggested as plasticizers for a vinyl chloride-vinyl acetate copolymer.²⁰³ Specifically, N,N.-dibutyl-8-(1,4,5,6,7-hexachloro-3-octylbicyclo[2.2.1]-5-heptene-2-yl)octanamide has been suggested. Halogenated cyclopentadiene-hexahalocyclopentadiene adducts have also been suggested as plasticizers, tackifiers, and insecticides.²⁰⁴

The Diels-Alder adduct between cyclooctatetraene and maleic anhydride has been esterified to form softeners for synthetic resins.²⁰⁵

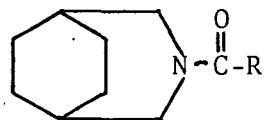


Esters of tricyclo[4.2.2.0^{2,5}]-dec-7-ene-3,4,9,10-tetracarboxylic acid dianhydride have also been used as plasticizers for polyvinyl chloride and other polymers.²⁰⁶

Bicyclic ester lactones such as (5-41) have been used as plasticizers for polyvinyl halides.²⁰⁷

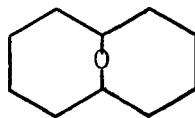


N-acyl imines derived from 3-azabicyclo[3.2.2]nonane have been



used as plasticizers.²⁰⁸ The N-decanoyl derivative has received special attention.

11-Oxabicyclo[4.4.1]heptadecanes have been suggested as intermediates



in the synthesis of solvents, plasticizers, and glycols.²⁰⁹

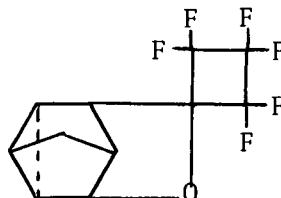
Adamantane derivatives that have been used as plasticizers are dihydroxyalkyladamantanes²¹⁰ and 1-adamantyl acetate,²¹¹ The latter compound is also proposed for use in perfumes.

Stabilizers

Most polymers are subject to slow degradation caused by sunlight. The addition of compounds to the polymer that can absorb ultraviolet radiation has been found to slow the rate of deterioration. Bicyclic and cage compounds have been used for this purpose and to increase the oxidative stability of polymers.

A mixture of β -pinene and 1,10-dithiodecane has been used to stabilized polyvinyl chloride.²¹² A 2 to 15% solution of these materials in the polymer was recommended.

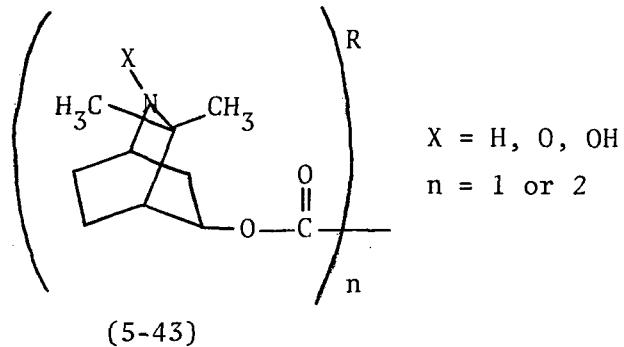
Alkyd resins are reported to have improved stability when (5-42) is added.²¹³



(5-42)

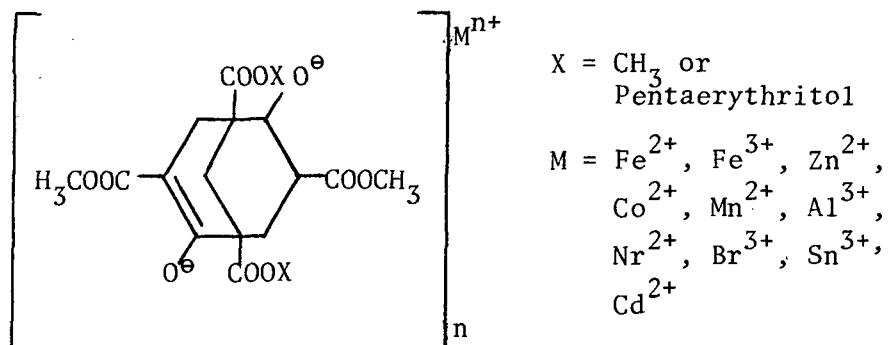
Similarly, the dipropyl, di-iso-butyl and dinonyl esters of 7-oxabicyclo-[2.2.1]-5-heptene-2,3-dicarboxylic acid have been used as light and heat stabilizers for vinyl and vinylidene polymers and copolymers.²¹⁴

Another class of general purpose ultraviolet stabilizers is (5-43).²¹⁵

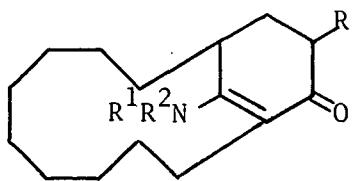


Triethylenediamine and derivatives have been used as an inhibitor for polymers of various types. Thus, triethylenediamine has been used as an ultraviolet and heat stabilizer for polyacrolein butyl acetol.²¹⁶ 2-Methyltriethylenediamine and 2-ethyltriethylenediamine have been used as oxidation inhibitors for poly(oxyalkylene).²¹⁷ The mono or di oxide of ethylenediamine has also been used as a polymerization inhibitor for the stabilization of organic compounds.²¹⁸

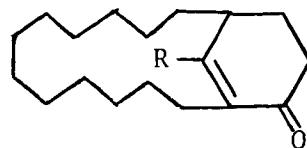
Metal bicyclononanes such as (5-44) have been used as resin inhibitors



for ultraviolet radiation.. Good results were obtained from phenol, vinyl and urethane resins.²¹⁹ Compounds (5-45) and (5-46) have also been used as ultraviolet light absorbers.²²⁰



(5-45)



(5-46)

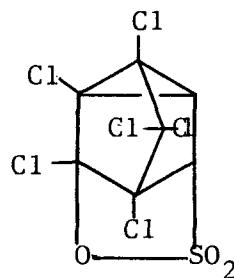
Preparation methods have been reported for the antioxidants 3-TK and TK-4 which are reported to give high stability to polyethylene-terephthalate and to rubbers. Neither the structure or the name of the additives was included in the abstract, but they are presumably bicyclic.²²¹

Flame Retardants

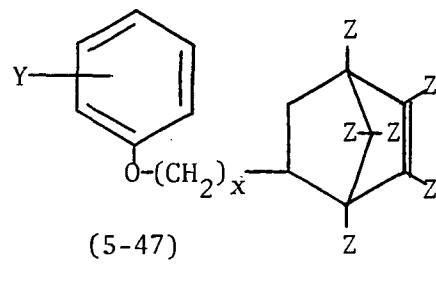
Flame retardance is usually imparted to polymers by the addition of materials containing phosphorous, halogens, or metal salts. The effectiveness, and general utility of these materials varies widely, and there is a continued search for new materials as polymers are incorporated into more and more products. All of the bicyclic flame retardants reported so far have been of the halogenated type. These have usually been derivatives of perhalogenated cyclopentadiene. The preparation, properties, and reactions of this class of compounds was studied extensively by E. T. McBee in the late 1940's and early 1950's.

Compounds of this type also generally show fungicidal and insecticidal activity, and many of the compounds discussed in the pesticide chapter (Chapter 7) could also be used as flame retardants. These compounds have not generally been crossreferenced in this report.

Sultones derived from hexachlorobicyclo[2.2.1]heptadiene have been suggested as flame retardants, fungicides, and insecticides.²²² The exact structure of the compounds is not known, but in one case the structure is believed to be:



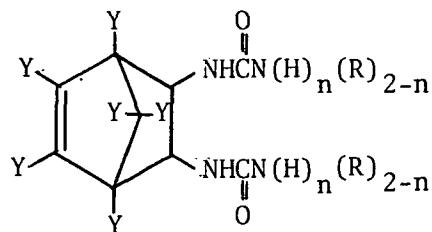
Halobicycloalkanyl aryl ethers of the general formula (5-47) have been proposed as useful in resins, plastics, pharmaceuticals



Z = halogen
 Y = $Z, H, NH_2, OH, CN, NO_2, SO_4$
 X = 0 or 1

insecticides and other products.²²³ Hexa-halobicyclo[2.2.1]hept-5-

ene-2,3-bis ureas have been treated with formaldehyde to form flame

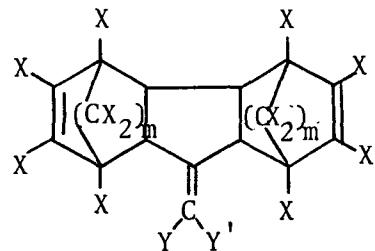


Y = F, Cl, Br

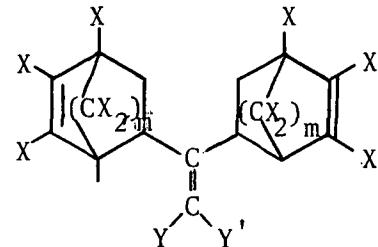
R = C₁-C₂₀ alkyl, cyclohexyl, phenyl, chlorophenyl, benzyl
n = 0, 1

retardant urea-formaldehyde resins.²²⁴ They have also been used as additives to impart flame retardancy to polyurethanes.

Two other types of compounds that have been proposed as flame retardancy additives are (5-48) and (5-49).²²⁵



(5-48)



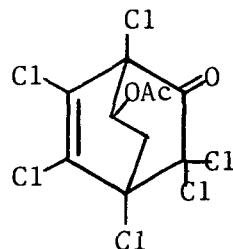
(5-49)

X = Cl, Br, H (at least 2 X's = Br or Cl)

Y, Y' = carboxy or carboxyalkyl

m = 1 or 2

Another compound²²⁶ is 1,3,3,4,5,6-hexachloro-2-keto-7-acetoxy[2.2.2]bicyclooctane 5.

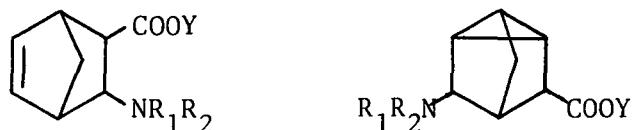


Monomers

Several bicyclic and cage compounds have been prepared that might find utility as monomers. A few of these are collected in this section to serve as a stimulation for new products. Obvious monomers that have been discussed in earlier parts of this chapter have generally not been included. No attempt has been made to be exhaustive in this section.

Bicyclo[2.2.1]heptanes

Aminobicycloheptene carboxylates and aminotricycloheptane carboxylates might be used in polyamides.²²⁷ Similarly, 2,3,4,5-tetraphenyl-

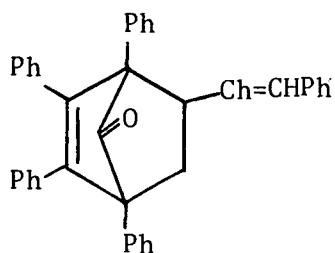


R₁ = hydrocarbon (C₁-C₈)

R₂ = H, R

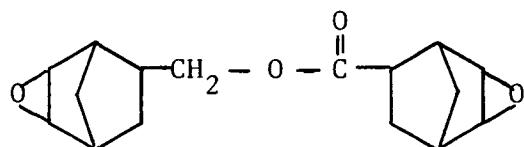
Y = alkyl with 1 to 5 carbons

1-(2-phenylvinyl)-8-ketobicyclo[2.2.1]-3-heptene might be useful in



the formation of polyolefins.²²⁸

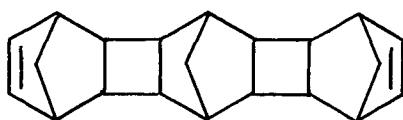
A possible monomer for use in epoxyresins is 5,6-epoxybicyclo[2.2.1]-heptan-2-ylmethyl-5,6-epoxybicyclo[2.2.1]heptan-2-ylcarboxylate.



This and similar compounds have been reported by Medved and Christie.²²⁹

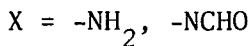
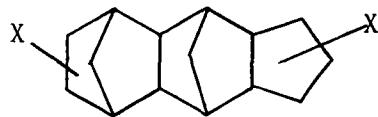
Non bicyclic polymers might be made from 7-oxabicyclo[2.2.1]heptane which was synthesized by Wittenberg.²³⁰

Zero valent nickel has been used to make dimers and trimers of



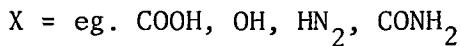
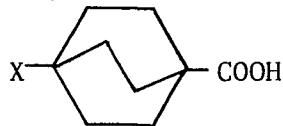
bicycloheptadiene.²³¹ These materials might be incorporated into

polyolefins. Tetrahydrotricyclopentadienyldiamines and the corresponding isocyanates have also been prepared, and may be useful as monomers.²³²



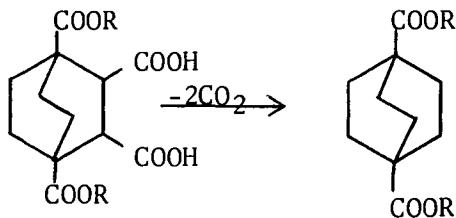
Bicyclo[2.2.2]octanes

Halta and Stock²³³ have studied the preparation and thermodynamic dissociation constants of 4-substituted bicyclo[2.2.2]octane-1-carboxylic acids.



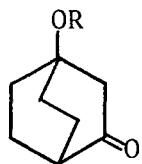
Kauer, Benson and Parshall²³⁴ have prepared compounds of this type by condensing ethylene with cyclohexa-1,3-diene-1,4-dicarboxylic acid.

Similarly, Chapman, Sotheeswaran, and Toyne²³⁵ have dicarboxylated compounds containing 2,3-dicarboxylic acids leaving 1,4 disubstituted products.



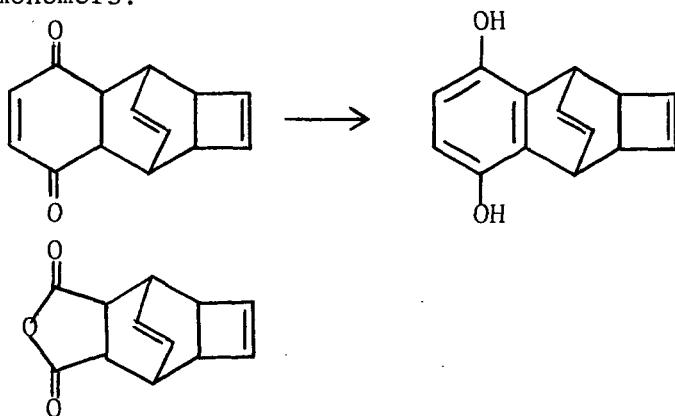
Some of these compounds should make useful monomers for the formation of polyesters, polyamides, and other polymers.

4-Alkoxybicyclo[2.2.2]octan-2-one has been prepared and suggested as a starting material for polymers and drugs.²³⁶



The corresponding 1-substituted compounds have also been reported.²³⁷

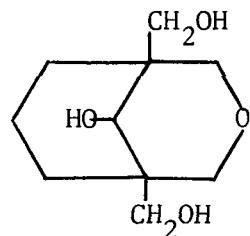
Benzoquinone and other adducts with cyclooctatetrene also might make good monomers.²³⁸



With these basic starting materials, a variety of possible monomers might be prepared.

Other Bicyclic Ring Systems

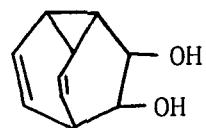
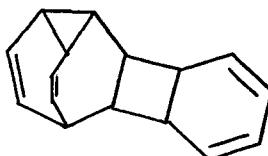
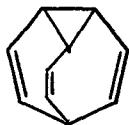
1,4-Diphenylbicyclo[3.2.1]oct-3-ene has been prepared as an intermediate in the manufacture of polymers.²³⁹ Another potential monomer is (5-50).²⁴⁰



(5-50)

This compound might aid in crosslinking polyester or other polymers.

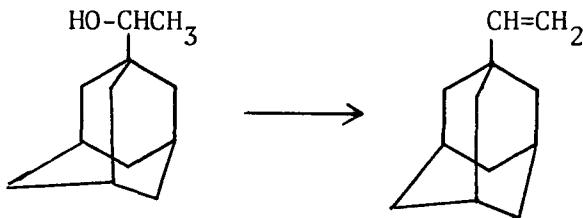
A series of polycyclic decanes has been prepared which are reported to have utility in polyurethanes, elastomers, synthetic fibers, alkyld resins, antifreeze, solvents and plasticizers.²⁴¹ Some examples are:



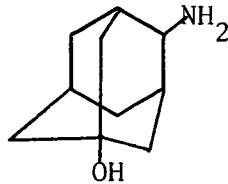
Sulfur containing monomers based on 1,5,9-cyclodecatriene has also been reported.²⁴²

Adamantanes

Adamantane-2-carboxylic acid and (2 adamantyl) acetic acid have both been synthesized.²⁴³ Esters of both of these compounds might be useful polymer additives. Similarly, adamantyl ketones have been prepared which might serve as intermediates for monomer or polymer additives.²⁴⁴ Vinyl adamantanes which are reported to be useful intermediates in the preparation of epoxyethyladamantane have been made from α -methyl-1-adamantanemethanol.²⁴⁵



Several new 1,4-disubstituted adamantanes have been prepared by Geluk and Schlatmann.²⁴⁵ An example is 4-amino-1-hydroxyadamantane.



5,7-Dimethyl-1,3-diaminoadamantane has also been reported.²⁴⁷

Miscellaneous Polymer Additives

A creaseproofing material for cellulose textiles has been formulated using bicyclopentadiene as one component of a graft terpolymer.²⁴⁸

Alkyl-N-(0-bicyclohexylcarbonates) have been found useful as modifiers and extenders for various synthetic resins.²⁴⁹ These compounds have also been found useful as fungicides, insecticides, and bactericides. The ammonium salt of N-dodecyl or N-octadecyl monamide of bicyclo[2.2.1]-5-heptene-2,3-decarboxylic acid has been used as an emulsifier for water thinned paints.²⁵⁰ Chlorinated camphor enolacetate and related bicyclic compounds have been used as plasticizers for nitro and aceto-cellulose.²⁵¹ 9-Amino-9-azabicyclo[3.3.1]nonane has been proposed as an antioxidant.²⁵²

Critique

Most of the obvious bicyclic and cage compounds that might be expected to form polymers have been prepared and polymerized. In general, these materials have been reported to produce polymers with improved thermal and oxidative stability.

Unfortunately, no uniform method of evaluating the improved properties has been used. Furthermore, in many of the patents covering these materials, the use of the compounds in polymers is only one of several uses suggested. In these cases, there is no experimentally based reason to believe that the compounds would necessarily make superior polymers.

There is reason to suspect, however, that at least a partial effort has been made to evaluate the area of bicyclic monomers for commercial value. This suspicion is based on the observation that a large number of patents and papers were issued during the early 1960's. DuPont in particular seems to have tried hard to make useful polymers with these compounds. In spite of this effort, it is not obvious that any bicyclic or cage polymer (except the p-xylylenes) has ever been commercialized.

If the improved thermal and oxidative stability that has generally been claimed for these compounds is significant, then some commercial effort would seem to have been appropriate unless some other necessary properties of the polymers are inferior. Since there is no evidence in the literature to indicate a technical problem, the lack of commercialization may be economic in origin.

An economic problem is easy to rationalize. The market for thermally and oxidatively superior polymers is probably not large since existing polymers are of good quality for most purposes. Thus, a large scale plant producing large quantities of the polymer could not be justified, and the polymer would probably have to command a premium price. The higher the price, the more the market would be restricted. With a small market, the cost of additional research and development work probably could not be justified by a large corporation.

A small company might be able to successfully manufacture some of the polymers described here if a market could be guaranteed and if it did not have to invest in extensive research to determine which products to make and how to make them.

If this reasoning is correct, and an organization such as NASA has a need for small, but significant quantities of thermally and oxidatively stable polymers, it will probably have to support the development work itself. To do this, it will have to prepare the polymers and evaluate them against a uniform test procedure that is relevant to its needs. If a formulation having sufficiently enhanced properties can be developed, then a monomer process development project will be needed to produce a commercially viable route to the product.

At this point, a small chemical company could probably be persuaded to manufacture the product to predetermined specifications if an initial market could be assured. The company could then support further process improvement as the market developed.

While bicyclic polymers have been fairly extensively studied, bicyclic polymer additives have not been studied as thoroughly. The use of bicyclic compounds as polymer additives seems to have been randomly explored, with no thorough attempt to organize the field. The phosphorous based flame retardants in particular have been completely ignored.

As an example, triphenyl phosphine oxide has been advertized as a heat stable phosphorous flame retardant. Replacing the benzene rings with bicyclo[2.2.1]heptane or bicyclo[2.2.2]octane rings should not significantly affect the size or shape of the molecule, but should increase the temperature stability and melting point of the product. While the phosphine oxide might be difficult to synthesize with the phosphorous at the bridgehead, the corresponding phosphite should be easy to make, and might be a useful additive. Other bicyclic compounds where the phosphorous is incorporated into the ring might also be useful.

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CHAPTER 5
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Part I: Triethylenediamines in polyurethanes

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Chapter 6 - Medicinal Applications

Bicyclic, tricyclic and higher cyclic compounds are used extensively in the field of medicine. The most common applications are as antivirals and antidepressants.

The 1-aminoadamantanes (symmetrel, amantadine) and their various derivatives represent the basic nucleus used to fight viral infections.¹ The bicyclo[2.2.2]octanes and various compounds derived from this nucleus possess the ability to alleviate depression brought on by various conditions. The miscellaneous applications can be found in almost any therapeutic area of medicine.

The use of bicyclic and cage compounds in medicine appears to be growing. This is probably due to their superior properties. For example, some compounds have been reported to be highly active yet have low toxicity. Others have prolonged activity because they are only slowly expelled from the body.

Analgesics

One of the greatest objectives in medicine has been to alleviate the suffering caused by pain. Analgesics are drugs with this pain relieving action and are classified as either narcotic or non-narcotic. This classification is one of legal considerations, and from a medical standpoint it would be more precise to classify the analgesics as either strong or mild. Most of the narcotic analgesics are strong, and most of the non-narcotic analgesics are mild.

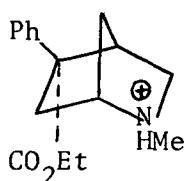
The analgesic action of the opiates has been known throughout history. Over the years the structure of these compounds have been

determined and a multitude of derivatives have been prepared. Many of these derivatives show analgesic action without the euphoriant and addictive effects that are normally observed with the narcotic analgesics.

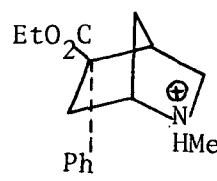
Recently, an opiate receptor has been described.² This receptor is said to be in nervous tissue and its proposed existence is based on structure-reactivity similarities of active opioid drugs, stereospecificity, and activity of the opiate antagonists. Tritiated naloxone is a specific example and has been found to bind in the nervous tissue of the brain.³

In contrast to the narcotic analgesics the non-narcotic analgesics usually possess antipyretic, and in some cases, antiinflammatory properties. Members of this family are the salicylates, pyrazolones, and analine derivatives with the newest members indomethacin and mefanamic acid. All members are analgesic, antipyretic, and only the aniline family does not possess antiinflammatory and antirheumatic properties. These analgesics are classified as mild due to their inability to reduce severe pain.

The bicyclic analgesic compounds fall into various categories. The first are the azabicyclo[2.2.1]heptane and bicyclo[2.2.1]heptane systems. The initial compounds in this series are the endo- and exo-2-methyl-5-phenyl-5-carbethoxy-2-azabicyclo[2.2.2]heptanes (6-1), (6-2).

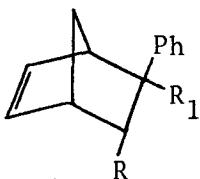


(6-1)



(6-2)

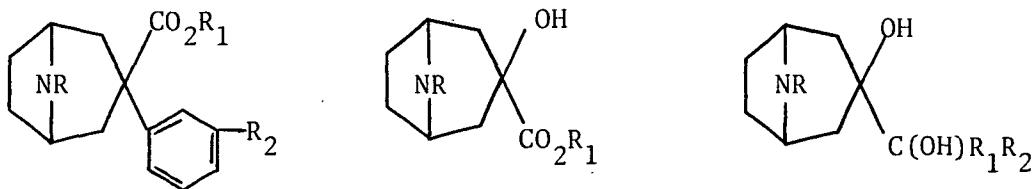
Physiochemical studies show that the endo-phenyl epimer (6-2) is six times more potent than the exo-isomer and two times more potent than meperidine (Demerol).⁴ The difference in geometry between the exo- and endo-isomers suggests different modes of interaction with an analgesic receptor. 2-Hydroxymethyl-2-phenyl-3-pyrrolidinylmethyl-5-norbornene was synthesized as a possible analgesic member of this class, but after pharmacological screening, it was found not to possess analgesic activity.⁵

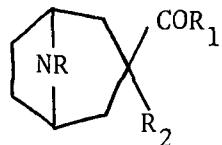
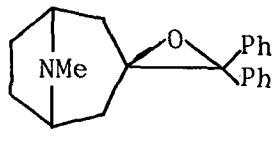


R_1 = Hydroxymethyl
 R = Pyrrolidinomethyl

The next highest homolog in the analgesic series is the general class of cyclic dicarboxycyclic imides of the bicyclo[2.2.1]-hept-5-ene and bicyclo[2.2.2]oct-5-ene series. A number of compounds of this type possessing analgesic and antispasmodic properties have been synthesized by Nakanishi, et al.⁶

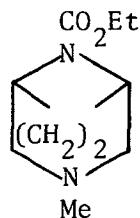
In the bicyclo[3.2.1] category are the 3-(monocarboxycyclic aryl)-3-carboxy tropanes and their various ester derivatives which are useful as analgesic compounds.⁷ Intermediates related to these compounds are



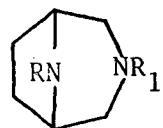


the anticholinergic and ganglionic blocking agents.

The 3-methyl-8-propinyl-3,8-diazabicyclo[3.2.1]octane system is reported to have the property of high analgesic activity.⁸



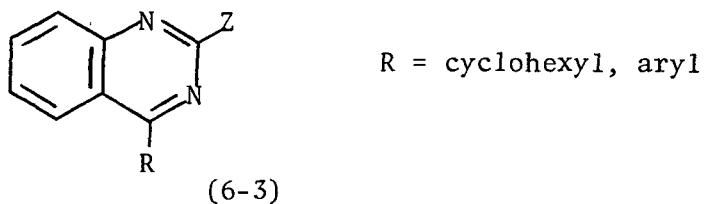
However, various differences in chemical and biological behavior are found between the 8-substituted-3-methyldiazabicyclooctanes and the corresponding isomeric 3-substituted-8-methyldiazabicyclooctanes. Another diazabicyclooctane analgesic compound in which R or R₁ may be an alkyl or acyl group, having properties other than analgesia, has been reported by S. Lepetit.⁹ These therapeutic activities include diuretic, central and peripheral nervous system depressant effects.



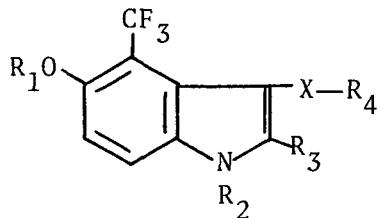
A synthetic method has been devised and derivatives prepared for the camphane series of analgesics.¹⁰ In this series, the most important derivatives showing marked analgesic effects are: N,N-dimethyl-2-

[(9-hydroxy-3-camphoryl)amino]acetamide, N,N-dimethyl-2-[(9-hydroxy-3-camphoryl)methylamino]acetamide, 3-methylamino-10-hydroxycamphor, and N,N-dimethyl-2-[N-(10-hydroxy-3-camphoryl)methylamino]acetamide.

2-Aminoquinazoline compounds and addition salts of the general formula (6-3) where R is various groups including 3-azabicyclo[3.2.2]non-3-yl have been prepared and are useful for their analgesic and antiallergenic properties.¹¹

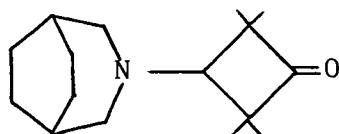


Similar to the aminoquinazoline compounds (6-3) elaborated above are the 3-substituted-4-trifluoromethylindoles which have analgesic activity themselves and also serve as intermediates for other biologically active indoles.¹² The bicyclic moiety, 3-azabicyclo[3.2.2]nonan-3-yl, is positioned at R₄.

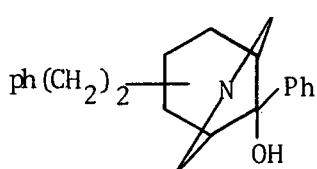


A substituted cyclobutanone has been prepared by Eastman Kodak Co. and serves as an intermediate in the preparation of analgesics

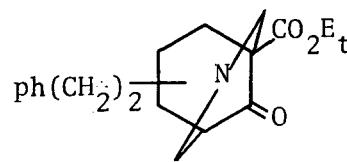
and dyeable polymers.¹³ The derivatives prepared include 2,2,4,4-tetramethyl-3-(3-azabicyclo[3.2.2]nonan-3-yl)cyclobutanone.



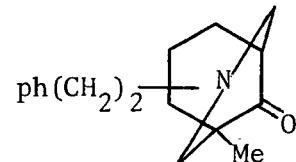
The last of the bicyclic analgesics are of the bicyclo[3.3.1]-nonane family. Iwai and Kurabayashi have described the synthesis of the 1-methyl-3-azabicyclo[3.3.1]nonane derivatives useful as analgesics.^{14,15} These derivatives include 1-methyl-3-phenethyl-9-hydroxy-3-phenyl-3-azabicyclo[3.3.1]nonane (6-4), 1-methyl-3-phenethyl-9-oxo-3-azabicyclo[3.3.1]nonane-5-carboxylate (6-5) and 1-methyl-3-phenyethyl-9-oxo-3-azabicyclo[3.3.1]nonane (6-6).



(6-4)



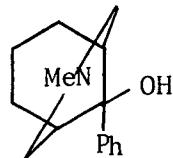
(6-5)



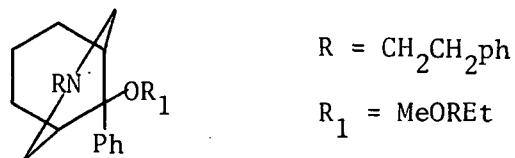
(6-6)

Similar to the above systems, (6-4), (6-5), (6-6), are the analgesic 3-methyl-9-hydroxy-9-phenyl-3-azabicyclo[3.3.1]nonanes. These

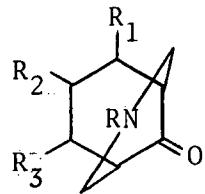
compounds and their acid addition salts have exceptionally high storage stability.¹⁶



High analgesic activity and low toxicity are the features of a similar series of compounds reported by Iwai, et al.¹⁷ The last in this series

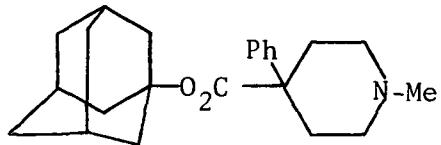


is the 9-oxo system reported to have an added antipyretic action.¹⁸



Although the 1-aminoadamantanes have been recognized for their antiviral activity, it has been reported that derivatives of these compounds have been prepared and tested for their analgesic, anti-inflammatory, and antipyretic properties.¹⁹ The adamantan-1-carboxylate analog of salicylic and anthranilic acid has also been prepared.²⁰ The synthesis of adamantyl analogues of narcotic analgesics

has been reported by Voldeng, et al.²¹ Preliminary studies with mice indicate that the ester hydrochloride salt is more potent and longer lasting than meperidine hydrochloride.



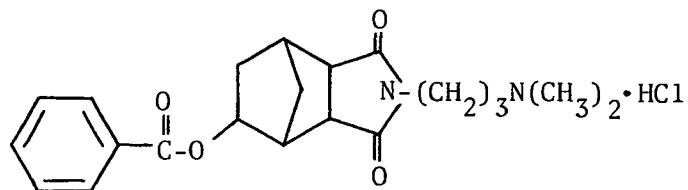
Antiarrhythmic Drugs

Disorders of cardiac rhythm are believed to arise as a consequence of electrophysiologic changes in the heart. Antiarrhythmic drugs act by normalizing or altering these disturbances. Heart impulses are generated by one of the two proposed mechanisms,²² the first of these being spontaneous discharge of a pacemaker cell at a particular site, and second, the re-entry mechanism. There is evidence to indicate that the various nerve fibers are actuated above normal by epinephrine, digitalis and low potassium ion concentration, and deactivated by the prototype antiarrhythmic drug, quinidine, or high potassium ion concentration.

Other antiarrhythmic drugs include procainamide, lidocaine, a local anesthetic used to treat ventricular arrhythmias, diphenylhydantoin, an anticonvulsant, propranolol, and potassium salts.

A new antiarrhythmic drug, BL-3677A (d-5-endo-benzoyloxy-N(dimethylaminopropyl)-bicyclo[2.2.1]heptane-2,3-endo dicarboximide hydrochloride), has been evaluated on experimental cardiac arrhythmias in

the dog.²³ BL-3677A reversed ouabain-induced ventricular tachycardia and markedly increased the amount of ouabain required for cardiac



toxicification. Additional properties of BL-3677A include prolonged conduction in the His-Purkinje system and ventricular muscle, and some local anesthetic activity.

The 1,5-diphenylbispidine derivatives, most notably 1,5-diphenyl-3,7-bis(B-diethylaminoethyl)bispidine-9-ol, have been compared to quinidine, a known antiarrhythmic drug, and were found to be more active *in vivo* and less active *in vitro*.²⁴

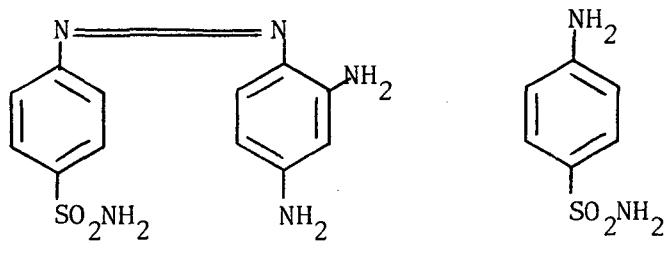
Boehme and Nichols have synthesized a new series of bicyclo[2.2.1]-heptane compounds which possess antifibrillatory activity besides antiarrhythmic properties.^{25,26} Included in the class of antiarrhythmic drugs are the antispasmodics. These drugs also effect the heart rhythm.^{27a,b,c,d}

Antibiotics and Antibacterials

Systemic bacterial infections could not be treated with drugs prior to 1935. Antiseptics and disinfectants were used topically to eradicate infections, but their unfavorable therapeutic index prevented their use as systemic agents. Topical uses included effective treatment of malaria, amebiasis, and spirochetal infections.

In 1935, prontosil, a dye, was reported to protect mice against a systemic streptococcal infection, and patients suffering from such an infection were also cured.²⁸ Prontosil itself was ineffective against the bacteria in the test tube, but the eradication of the systemic infections in living systems proved to be a milestone in the history of chemotherapy.

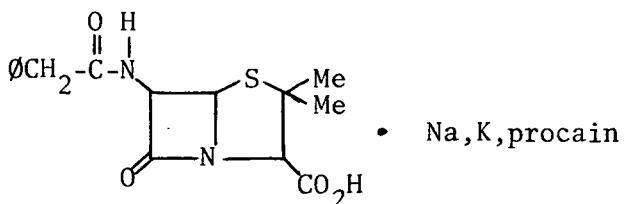
Later, it was discovered that prontosil is broken down in the body to give p-aminobenzenesulfonamide, later described as sulfanilamide. Sulfanilamide, in turn, was demonstrated to be the active breakdown product. In time, numerous derivatives of sulfanilamide were prepared,



and a host of systemic infections succumbed to the actions of these new drugs. The treatment of these infections lead to new discoveries about bacterial metabolism. Biologic antagonism, carbonic anhydrase inhibitors, and antithyroid drugs are examples of the various areas revealed to scientists by the study of the sulfonamides.

The success in treatment brought on by the sulfonamides revived interest in the antibiotics, or those compounds produced by micro-organisms used to inhibit the growth of other microorganisms. One of the most remarkable observations of antibiosis was Fleming's discovery that Penicillium mold and the culture filtrates of this mold prevented

the multiplication of staphylococci.²⁹ A team at Oxford, led by Florey, succeeded in separating a concentrate of this antibacterial factor and its pronounced activity and lack of toxicity were demonstrated.^{30,31}



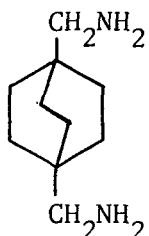
Penicillin G

The potency and lack of toxicity of penicillin turned investigators to search for more sources of antibiotics. In a short time, numerous antibiotics were prepared. Some were too toxic for clinical applications, but from this research came welcome additions to therapeutics, such as streptomycin, the tetracyclines, chloramphenicol, and neomycin.

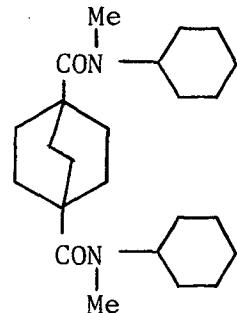
Compounds having the bicyclic structure have been used in various antibacterial compositions. The 1,4-diazabicyclo[2.2.2]octane (triethyl-enediamine) system has been used to prepare dimerized propiolate esters which show bacteriostatic action against Bacillus subtilis and Saccharomyces cerevisiae.³² A series of dithiocarbonic acid esters have been prepared which show activity against bacteria, fungi, and coccidia.³³ These derivatives are prepared from the formaldehyde adduct of an amine with carbon disulfide or from the substituted thiocarbonate with the formaldehyde adduct of the amine. The 2-(2-azabicyclo[2.2.2]octyl) moiety serves as an amine. The 1,4-bis-cyclic and -arylamino bicyclo[2.2.2]octane derivatives have been prepared and are useful antibiotics against both gram-positive and gram-negative bacteria.³⁴

These compounds serve also to lower cholesterol levels in the blood.

Among the compounds prepared are 1,4-bis(aminomethyl)bicyclo[2.2.2]octane (6-7) and N,N'-dicyclohexyl-N,N'-methylbicyclo[2.2.2]octane-1,4-dicarboxamide (6-8). Useful antibacterials of the same general structure of



(6-7)



(6-8)

(6-7) and (6-8) are the bicyclo[2.2.2]octane derivatives shown below.³⁵

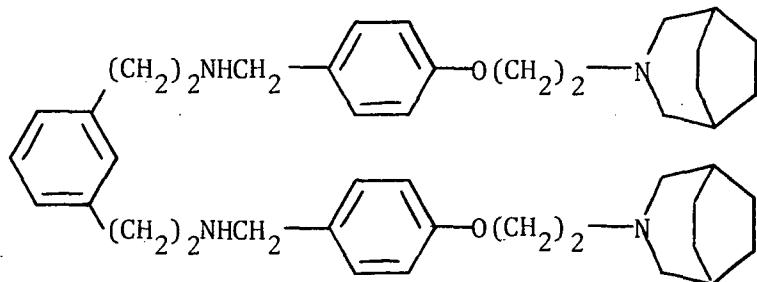
These derivatives also possess the ability to reduce the levels of



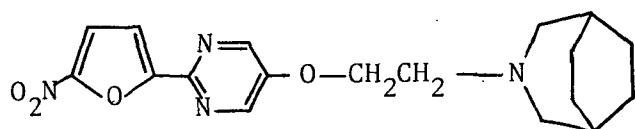
cholesterol in the blood.

Antibacterial bicyclo[3.2.2]nonane derivatives have been reported.

The first of these derivatives are the arylalkylamine compounds with

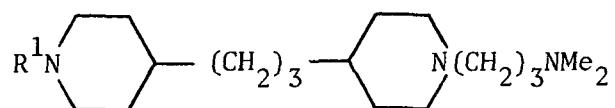


the 3-aza-3-bicyclo[3.2.2]nonyl group attached.³⁶ Another antibacterial compound that also has trichomonicidal properties has been reported by Gutsche, et al.³⁷ Among 16 compounds prepared was the 3-azabicyclo[3.2.2]nonan-3-yl derivative.



A broad-spectrum antimicrobial using the general class of 3-acyl-alkyl-3-azabicyclo[3.2.2]nonane nucleus has been prepared.³⁸ The antimicrobial activity exhibited is used against Staphylococcus aureus, Escherichia coli and others. Mannich bases with antimicrobial activity have also been reported and inhibit the growth of such microbial species as Saccharomyces cerevisiae, Escherichia coli, and Staphylococcus aureus.³⁹

The antibacterial bis(biperidyl) alkanes exhibit general pharmaceutical, antibacterial and antiparasitic properties.⁴⁰



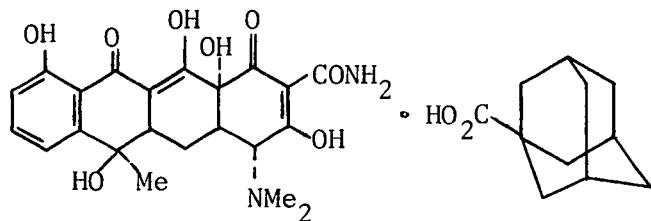
(6-9)

The adamantylcarbonyl derivative of (6-9) has been prepared. This patent also includes the method of preparation of the tablet forms and thin-

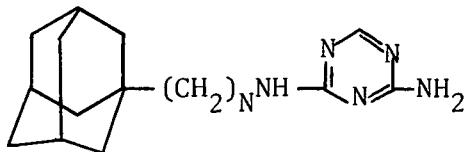
layer chromatography data. Sarbach, et al have reported the use of the adamantanecarbonyl group in their antibacterial and fungicidal 3-(5-nitro-2-furyl)-2-bromopropenal acylhydrazones.⁴¹



The well-known antibiotic tetracycline has been prepared as an adamantoate salt. This tetracycline adamantoate salt has been demonstrated to be effective against gram-positive, gram-negative, and rickettsiae organisms.⁴² Also there are pharmacological, spectral,

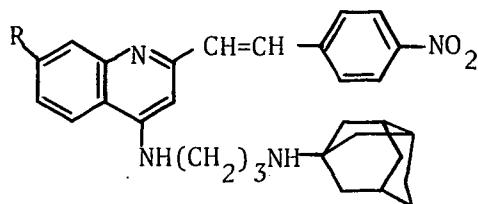


and antiviral data given. The antimicrobial adamantyl-s-triazine synthesis has been reported by Narayanan,⁴³ and various derivatives

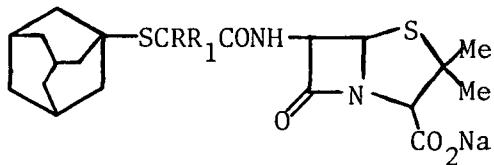


have been prepared. These compounds also have hypoglycemic properties. The last in this series is the 4-[[[3-adamantylamino)-propyl]amino]-7-chloro-2-(p-nitrostyryl)quinoline derivatives where R=1-adamantyl.

These compounds have antibacterial and antiviral properties.⁴⁴

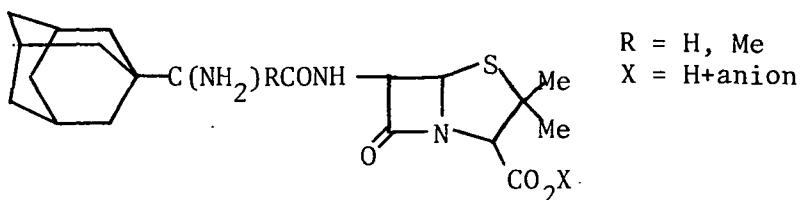


The last of the antibiotics and antibacterials are the penicillins and sulfanilamides. Concerning the penicillins, the general synthesis of 6-aminopenicillanic acid derivatives has been reported.⁴⁵ The most important compound prepared is the $\text{Na}\text{-}6\text{-}(1\text{-adamantylcarbonylamino})\text{-penicillinate}$. Also used were the 3-substituted-adamantane-1-carbox-cyclic acids (R=F, Cl, MeO, HO, CO₂H, Br, I, Ph). Also, various bicyclo[2.2.1]-heptanes, bicyclo[2.2.2]octanes, and tricyclo[4.3.1]undecanes were used. These penicillins were active against strains of Staphylococci. Another general synthetic route has been devised and the $\alpha\text{-}(adamant-1-ylthio)\text{-alkylenicillins}$ have been prepared.⁴⁶ No special properties have been reported for these systems.



Hermann and Snyder have reported the synthesis of $\alpha\text{-amino-1-adamantylmethylpenicillins}$.⁴⁷ These penicillins exhibit excellent

acid sensitivity and resistance to penicillinase, an important step in the treatment of bacteria that produce penicillinase.



A similar penicillin derivative that is also resistant to penicillinase has been prepared by Loevens Kemiske Fabrik Produktionsaktieselskab.⁴⁸ These 3-amino-1-adamantylpenicillins are broad spectrum antibiotics used against Staphylococcus aureus, Escherichia coli, Proteus mirabilis and a host of others. Serum levels as compared in rat and man (to methicillin and penicillin-G-Na) are also reported. The 1-amino-adamantane benzylpenicillin salt prepared by Galardo has been observed to have slow release activity.⁴⁹ This is highly important because penicillins can be broken down by gastric juices and the absorption of this antibiotic is poor in the gastrointestinal tract.⁵⁰ Related to this is the antibiotic action and better absorption in organisms of α -aminobenzylpenicillanic acid esters.⁵¹ These penicillin compounds include the 1-adamantylcarboxymethyl derivative. The last of the penicillin derivatives, prepared by J. R. Gieg A.-G.⁵² have been reported to be used when bacterial strains resistant to penicillin-G are found.

The spectacular results observed in the penicillin family by preparing various derivatives have not been observed in the sulfanilamide family. Narayanan⁵³ has prepared new antimicrobial N'-(1-adamantylalkyl)-

sulfonamides. Among the derivatives prepared was N-(1-adamantyl)-p-nitrobenzenesulfonamide and N'-(1-adamantyl)sulfonamide. A new series of sulfonamides has been prepared by Daeniker.⁵⁴ These new compounds include 1,4-endomethylene-3-phenyl-cyclohexane-2-sulfonamide, and 1,4-endoethylene-5,6-oxido-cyclohexane-2-sulfonamide.

The last of the sulfonamides in this series are the sulfonamides containing the adamantyl radical. These compounds were prepared to determine the effect on microbial activity by the large adamantyl group.⁵⁵ However, none of these compounds showed any antibacterial activity.

Anticancer Drugs

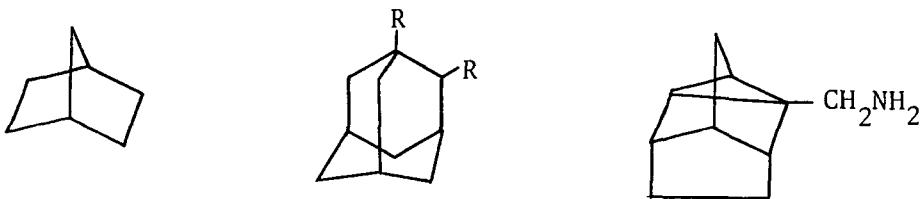
Although the antineoplastic agents, or anticancer drugs, have not had the dramatic impact on medicine of the antibacterial drugs, they are becoming increasingly important. Leukemia, malignant lymphoma, multiple myeloma, and carcinomas have been treated successfully with these drugs, and some cures have been reported.⁵⁶

The drugs currently used in anticancer chemotherapy are generally highly toxic and not very selective. Consequently, their therapeutic index is quite low. The most recent emphasis in cancer chemotherapy is the application of synergistic combinations of the various chemotherapeutic agents coupled with a knowledge of the cell cycle on which these agents act. Using this technique, the life expectancy of children with acute leukemias has been increased, and disseminated choriocarcinoma in young women has been cured.⁵⁷

The various anticancer drugs fall into the following categories:

1. Alkylating agents
2. Antimetabolites
3. Hormonal agents
4. Radioactive isotopes
5. Antibiotics and miscellaneous

The bicyclic and cage compounds found in anticancer drugs are generally antimetabolites, but some compounds in other categories such as the alkylating agents are also found. The bicyclic and cage compound used in cancer chemotherapy include the classes of bicyclo-[2.2.1]heptanes, adamantanes, and miscellaneous polycyclics.



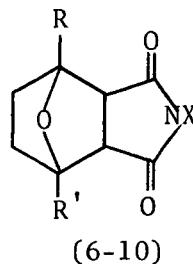
Bicyclo[2.2.1]heptanes

Pettit, et al⁵⁸ have prepared 1,4-bis-(2-chloroethyl)-1,4-diazonia-bicyclo[2.2.1]heptane dichloride, a novel quaternary ammonium salt. Information concerning the chemical and physical aspects of this new ring system has been summarized in this report. ¹H nuclear magnetic resonance data are also available.

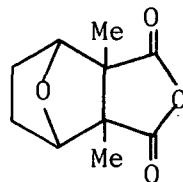
Thirteen potential anticancer bicyclic nitriles and related compounds have been formulated by Scheiner and Vaughn.⁵⁹ These new compounds were made available by Diels-Alder cycloaddition reactions involving fumaronitrile, maleonitrile, acrylonitrile, and tetracyanoethylene as dienophiles and cyclopentadiene, cyclohexadiene, cycloheptadiene, and cyclooctatetraene as dienes.

Grogan and Rice⁶⁰ have produced a series of 7-oxabicyclo[2.2.1]-heptane-2,3-dicarboximides (6-10) and studied their pharmacological

activities. Some of the compounds also demonstrated pharmacological properties other than anticancer activity.



Similar to (6-10) is cantharidin. This homeopathic anticancer



agent has been described by Baranger⁶¹ and is especially active against lymphoma in chickens.

Bicyclo[3.2.2]nonanes

The preparation of halogenated aminobisphenols as possible carcinostatic agents has been reported by Shaner and Meadow.⁶² Among these compounds is the 3-azabicyclo[3.2.2]nonane derivative.

Adamantanes

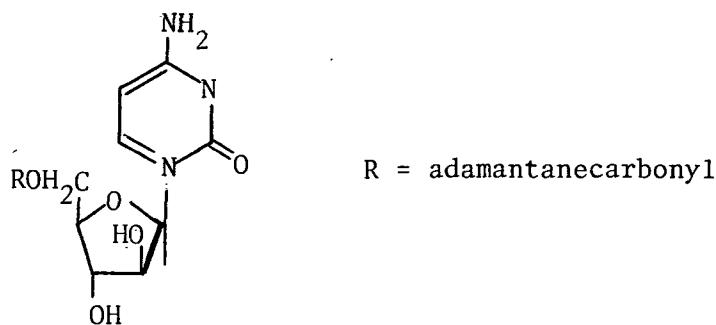
The various anticancer agents containing the adamantane functional group include the classes of antitumor, antileukemic, and anticarcinomatous agents.

D-Arabinofuranosylcytosine is known to control the growth of certain tumors. Wiley and Neil⁶³ have prepared 1- β -D-arabinofuranosylcyto-

sine-5'-(1-adamantane carboxylate) and 5'-O-adamantoyl-D-arabinofuran-oxylcytosine. These two compounds are reported to be highly potent and are absorbed at a uniform rate. Consequently, these derivatives are more suitable as depot agents. Niel, et al⁶⁴ have also described the use of various treatment schedules for the 1- β -D-arabinofuranosyl-cytosine derivative.

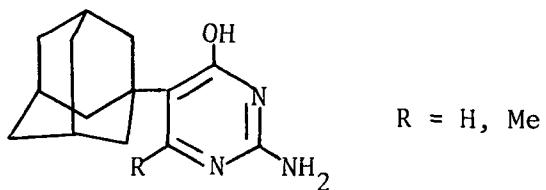
1-Adamantanamine hydrochloride and six derivatives prepared by Kolymkova⁶⁵ have been tested for their inhibitory and antiblastic actions on human normal and tumor cells. Angiosarcoma As, pancreatic carcinoma CaPa, and others were subject to sensitivity tests. Angiosarcoma line As and pancreatic carcinoma CaPa were most sensitive to 1-(acetyl amino)-adamantane and 1-(methyl amino)adamantane. 1-Adamantanamine produced sensitivity in cells from lines 709 and CaVe. 1-(Dimethyl amino)adamantanane and 1,5-bis-(N-methyl adamantanino)pentane dimethobromide were not seen to selectively act on tumor cells. The least toxic compound reported was 1-(diethyl amino)adamantanane hydrochloride.

The 5'-O-derivatives of aracytidine have been synthesized by Kelly, et al⁶⁶ and are effective drugs against leukemia. Among the 30 compounds prepared is the adamantanecarbonyl derivative.

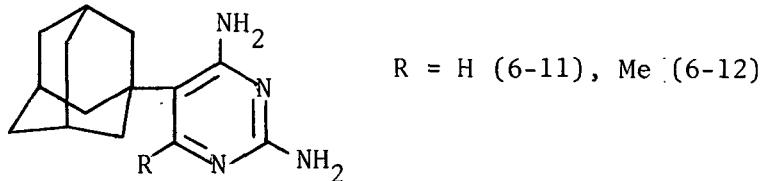


Amantadine, an immunosuppressive agent, was given to patients during active immunotherapy for acute lymphoblastic leukemia and was found to inhibit the effects of this treatment.⁶⁷

The synthesis of 5-(1-adamantyl)-pyrimidines has been reported by Jonak, et al.⁶⁸



These compounds moderately inhibited mouse sarcoma 180 cells, and mouse mammary and adenocarcinoma. The authors also prepared 5-(1-adamantyl)-2,4-diaminopyrimidine (6-11) and 5-(1-adamantyl)-2,4-diamino-6-methylpyrimidine (6-12) analogues.⁶⁹

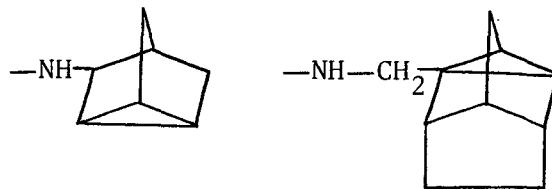


$$(6-11) = H \quad (6-12) = M_E$$

Both (6-11) and (6-12) showed exceptionally high activity toward mouse mammary adenocarcinoma cells (TA3) in culture. 5-(1-Adamantyl)-2,4-diamino-6-methylpyrimidine inhibited cell growth as effectively as methotrexate, a folic acid antagonist.

Miscellaneous polycyclics

Peterson, et al.⁷⁰ have synthesized about 300 derivatives of 2-amino-1,4-naphthoquinone and related compounds. These compounds were investigated for their carcinostatic activity. Relationships between structure and reactivity were considered. The carcinostatic quinones were particularly effective against Ehrlich carcinoma and Crocker carcinoma 180 of the mouse. Among the compounds tested were the tricyclo-[2.2.1.0^{2,6}]heptane and tetracyclo[2.2.1.2^{3,5}.0^{2,6}]nonane derivatives.



Anticholinergics

Smooth muscle spasm and the action of hydrochloric acid contribute to pain in peptic ulcer and possibly to its perpetuation. The anticholinergics reduce smooth muscle spasm and may also reduce the secretion of hydrochloric acid. Basically, these drugs are tertiary or quaternary amines related to atropine.

The advantages of the quaternary anticholinergics are claimed to be reduced central nervous system side effects and possible ganglionic blocking action. The ability to block the vagus through peripheral anticholinergic effects is also claimed. Although large doses can block gastrointestinal motility and hydrochloric acid production, there are some side effects. These include blurred vision, dryness of the mouth, and micturition difficulties.

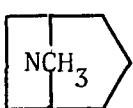
The bicyclic and cage compounds shown to have central or peripheral anticholinergic activity fall into the classes of the bicyclo[2.2.1]-heptanes, bicyclo[3.3.1]nonanes (granatanes), bicyclo[3.3.2]decanes, and the tricyclic[3.3.1.1^{3,7}]decane (adamantane) compounds.

Bicyclo[2.2.1]heptanes

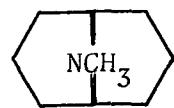
Hass and Klavehn⁷¹ have synthesized 3-piperidino-1-phenyl-1-(bicyclo[2.2.1]hept-5-en-2-yl)-1-propanol (Akineton). Akineton tests on isolated guinea pig intestine and blood pressure in the cat showed that this compound is an effective anticholinergic drug. However, Akineton is most efficacious in suppressing convulsions produced by nicotine in mice and rabbits.

Bicyclo[3.3.1]nonanes

The granatane derivatives, homologues of tropane, are reported to have potent anticholinergic activity.



tropane



granatane

However, these compounds have not been used extensively due to the strong side effects. Yoneda, et al⁷² have synthesized and tested the 6,6- and 7,7-gemdialkyl-9-azabicyclo[3.3.1]nonane derivatives. These compounds were prepared in an attempt to improve the pharmacological activities of the 9-azabicyclo[3.3.1]nonane system. The authors indicate that various glycolate derivatives had strong central anti-

cholinergic activity, and that high central specificity was imparted when gem-dialkyl groups were introduced onto the 9-azabicyclo[3.3.1]-nonane skeleton.

Ribbentrop and Schaumann⁷³ have conducted a study of granatane compounds. In a comparison to known anticholinergics, atropine, scopolamine, biperidine and benactyzine, the most active compounds, were demonstrated to be the granatanol-3-esters. Ester derivatives of N-(β -hydroxyethyl)-norgranatane have been prepared from benzilic, and substituted benzilic acid, methyl esters, acid chlorides, and chloro acid chlorides. These compounds show central and peripheral anticholinergic activity.⁷⁴ Stach, Dold, and Schaumann^{75a,b,c,d} have published a series of patents dealing with the synthesis of granatoline and 3 β -granatol derivatives of ethers and esters. C.F. Boehringer and Soehne have also prepared the nortropane, N-(hydroxyalkyl)-norgranatane and 3 β -norgranatol ester derivatives in this series.^{76a,b,c} Martell and Soine⁷⁷ have synthesized 3-hydroxy-1-azabicyclo[3.3.1]nonane and have investigated certain of the ester derivatives as potential anticholinergics. Results of this investigation have not been further reported.

Bicyclo[3.2.2]nonanes

Anticholinergics can antagonize or reverse motor incoordination. Tremorine or oxotremorine induced muscular rigidity and akinesia in mice, which renders them unable to remain on a rotating rod, has been shown to be reversed by a new potent, centrally acting and anticholinergic drug. This drug, SC-13639 (2,3-diphenyl-4-(3-azabicyclo[3.2.2]non-3-yl)butyramide hydrochloride), was discovered to be more potent, longer

lasting, and possess twice the separation of anticholinergic and loco-motor stimulant actions.⁷⁸

Adamantane derivatives

The 1-adamantanecarboxyclic acid ester of scopolamine has been reported to be a powerful anticholinergic.⁷⁹ It is prepared by allowing 1-adamantanecarbonyl chloride to react with scopolamine hydrobromide and then treating the solution with hydrochloric acid.

Antidepressants

Prior to the 1950's, there existed no pharmaceutical agents that could counteract depression. Consequently, psychotherapy and electro-convulsive therapy were the main forms of treatment for this condition.

Toward the late 1950's, the first pharmaceutical agents were developed and most were classified as monoamine oxidase (MAO) inhibitors. This classification is used due to the ability of these compounds to inhibit metabolic oxidative deamination of amines such as dopamine and tyramine. Dibenzazepine derivatives were discovered later to be useful in treatment of depressive syndromes.

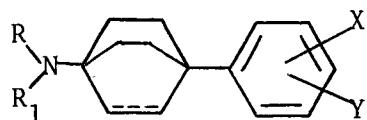
Imipramine (Tofranil), a tricyclic antidepressant, was discovered by accident while clinical tests for antipsychotic activity were being conducted.⁸⁰ This drug was followed by others such as amitriptyline and protriptyline and their demethylated metabolites such as desipramine and nortriptyline.

The mechanism by which these drugs act is attributed to the catecholamine hypothesis.⁸¹ The various antidepressants are said to increase the effective catecholamine levels in the central nervous system,

and the tricyclic antidepressants such as imipramine interfere with the uptake of catecholamine after its release from the nerve endings.

As a class of antidepressant compounds, bicyclic and cage compounds have been shown to effectively antagonize tetrabenzeno-induced sedation in mice, and potentiate the norepinephrine and phenethylamine pressor effect in ganglion-blocked anesthetized dogs.

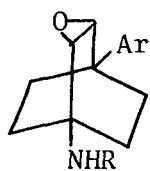
The bicyclic antidepressants have the general formula



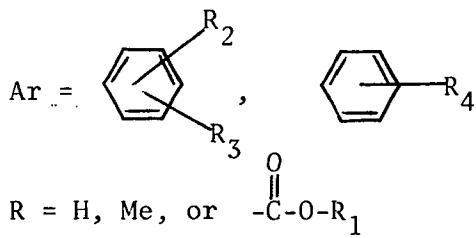
in which R, R₁, X and Y are the various constituents, and the dashed line represents a possible double bond. The phenyl group at the 4-position may be substituted with pyridyl or cyclohexane, and either of these groups may themselves be substituted, generally at the 4-position.

Bicyclo[2.2.2]octane derivatives

The first of these compounds are the 5-aryloxatricyclo[3.2.2.0^{2,4}]-nonan-1-yl urethanes⁸¹ of the general formula (6-13):



(6-13)

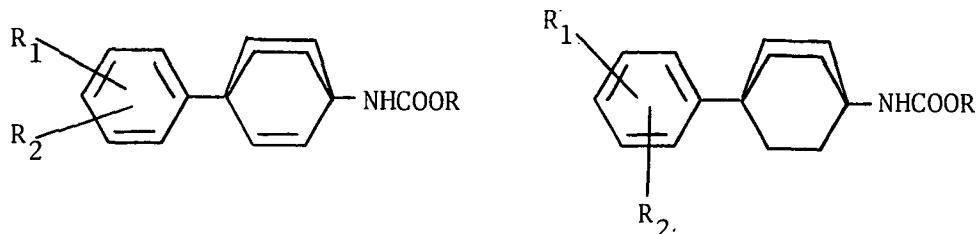


R = H, Me, or $-\text{C}(=\text{O})-\text{O}-\text{R}_1$
 R_1 = Alkyl (1 to 8 carbons), N,N-dimethyl-2-aminoethyl, ethylpyrrolidinyl, 2-methoxyethyl, benzyl

These compounds may be synthesized by converting the appropriate 4-aryl bicyclo[2.2.2]oct-2-ene-1-carboxycyclic acid to the corresponding azide followed by a modified Curtis Reaction to form the isocyanate. The isocyanate is then treated with an alcohol to form the corresponding urethane.

The compounds of formula (6-13) that are most preferred are those in which Ar is an unsaturated phenyl or pyridyl, R is $\text{-CO}_2\text{R}_1$, and R_1 is an alkyl group of 1 through 4 carbon atoms. These compounds show the best antidepressant activity in warm-blooded animals.

Similar compounds having the same antidepressant activities are the 4-aryl bicyclo[2.2.2]oct-1-yl urethanes that are used as pharmaceutically active agents.⁸³ Generally, these compounds have the following basic structures:

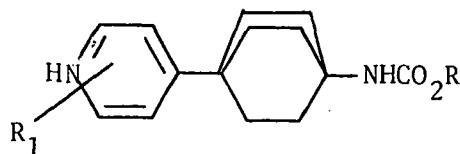


$\text{R} = \text{Alkyl 1 to 8 carbons, Et, pyrrolidinyl, } \emptyset\text{-CH}_2\text{-}$

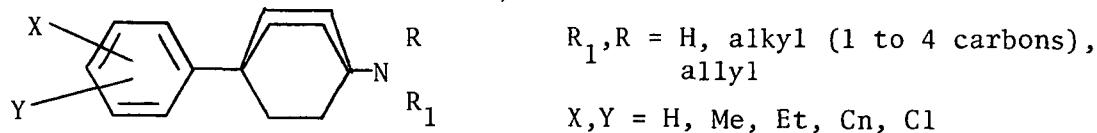
$\text{R}_1\text{R}_2 = \text{H, Me, Et, Cl, Br, F, NO}_2, \text{ amino, dialkylamino}$

The non-toxic anion salts of these compounds are also included in the context of these patents. Also substituted at the Ar group is a pyridine ring with various substituents.⁸⁴ These compounds have the

general formula:

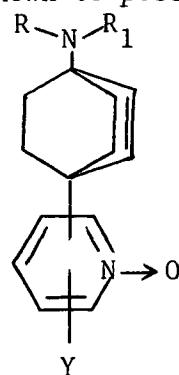


A similar series of compounds have also been shown to produce anti-depressant effects in warm-blooded animals.⁸⁵ These compounds also have the bicyclo[2.2.2]octane nucleus (6-14).



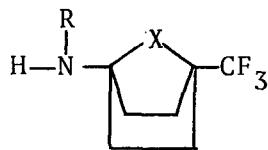
(6-14)

The aromatic ring at position 4 may also occur as a cyclohexyl structure having similar antidepressant actions. The substituents are the same as (6-14),⁸⁶ and a dosage method is also available for the administration of this antidepressant.^{87a,b} The sulfuric, tartaric, maleic, succinic, and mandelic, or lactic acid salts can also be prepared.⁸⁸ A variation of structure (6-14) having a pyridine ring substituted at the 4-position has also been shown to possess antidepressant properties.⁸⁹



Also included in the scope of this patent are the salts of the free amine derivatives.^{90a,b} An orally ingestible capsule and tablet form may also be prepared.⁹¹

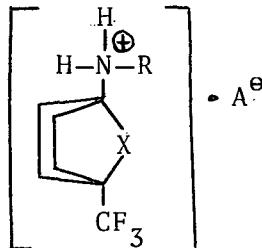
4-Trifluoromethylbicyclo[2.2.2]octane-1-amines and oct-2-ene-1-amines showing antidepressant activity have been prepared by Gregory and Whitney.⁹² These compounds have the general formula (6-15)



(6-15)

where R is hydrogen, methyl, or ethyl, and X is $-\text{CH}_2\text{CH}_2-$ or $-\text{CH}=\text{CH}-$.

Also prepared were the salts of (6-15)

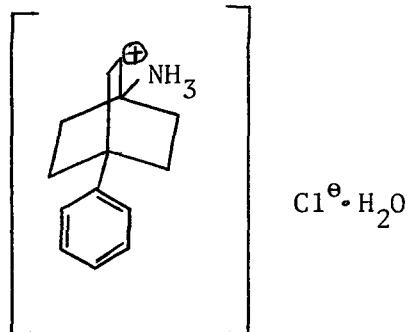


where R and X are the same as in (6-15) and A^{\ominus} is a nontoxic anion.

Various laboratory studies involving the prediction of antidepressant activity, metabolism, and physiology of bicyclic and cage compounds have been carried out.

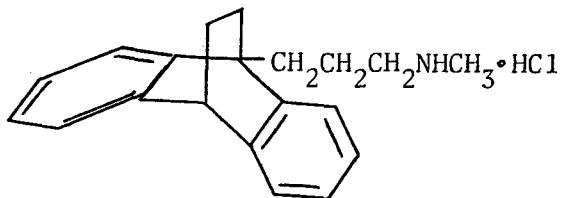
In a study conducted by Sanghvi, et al.⁹³ it was concluded that some agents shown to have antidepressant qualities in the reversal of sedation or rodent hypothermia, demonstrated no apparent clinical

antidepressant activity. Among these antidepressants is Exp-561 (4-phenylbicyclo[2.2.2]octan-1-amine hydrochloride monohydrate).



Tetracyclic compounds

A tetracyclic compound, Maprotiline, has been reported to possess antidepressant properties.⁹⁴ This antidepressant has the general



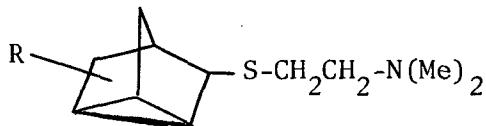
ability to antagonize tetrabenzeno-induced sedation, has similar effects to imipramine (inhibition of hypothermia), and contains the capacity to provoke depletion of cerebral catecholamines. This tetracyclic compound is reported to be the first of its kind, and may have a substantially different mode of action on the metabolism of serotonin than the typical tricyclics.

Another tetracyclic antidepressant, Tolyon, is reported to have similar effects to that of Maprotiline even under acute and chronic administration.⁹⁶ Following acute administration, the concentration of brain monoamines was reduced in the brain for several hours. Chronic

administration increased the concentration of brain normetanephrine. The pharmacological actions of Tolvon suggests that it acts on tryptaminergic receptors in the brain and acts on the central nervous system in a manner similar to minor tranquilizers.⁹⁷

Tricyclic compounds

A tricyclic compound 3-(diethylaminoethylthio)-nortricyclene



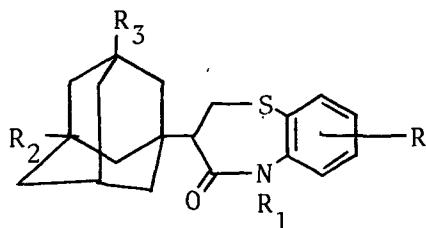
R = H, alkyl, alkoxy, halo, haloalkyl

has been reported by Gray and Heitmeier⁹⁸ to have antidepressant action. This compound and its derivatives also have utility as bronchodilators.

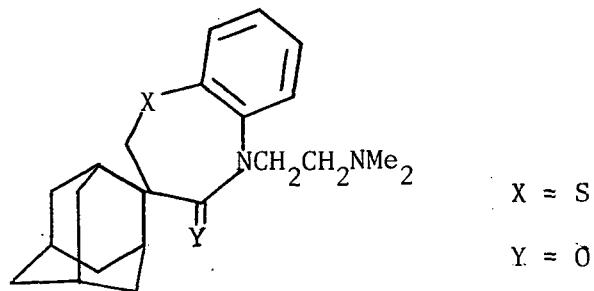
The effects of tri- and tetracyclic antidepressants on the heart and circulation has been studied.⁹⁹ It has been determined that when administered in recommended dosages for three weeks some tetracyclic antidepressants had no decisive influence on blood pressure or heart rate.

Adamantane derivatives

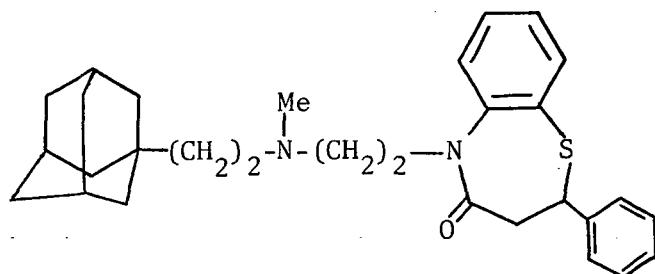
Commercial pharmaceutical preparations of various adamantane compounds have been reported by Squibb & Sons. Among the numerous derivatives are the adamantylbenzothiozepinones,^{100a}



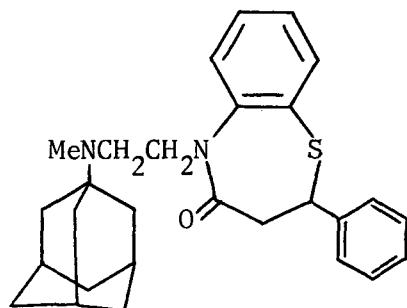
the spiro-[adamantane-2,2'-(3'H)-1].5-benzothiazepine compounds,^{100b}



the 2,3-dihydro-5-[2-(N-methyl-1-adamantylamino)ethyl]-2-phenyl-1,5-benzoxazepin-4(5H)ones,^{100c}



the adamantylamino phenyl-1,5-benzothiazepine derivatives,^{100d,e}



and the 2-(1-adamantyl)-5-(aminoalkyl)-1,5-benzothiazepines.^{100f}

Antifibrinolytic Agents

The role of fibrinolysis in the maintenance of blood fluidity has been known since the turn of the century. The groundwork for understanding the chemistry and biochemistry of the process was first developed during the early 1930's. The development of agents that could dissolve intravenous thrombi followed. These compounds are called antifibrinolytic agents.

Naturally occurring circulating fibrinolytic inhibitors regulate hyperfibrinolysis in the human. Synthetic inhibitors, provided by recent advances, neutralize excessive fibrinolysis and permit clinical management of bleeding that may be induced by the excessive pathological fibrinolysis.

In the complement mechanism, the conversion of the first component of complement C_1' to C_1' esterase (the active proteolytic enzyme) is closely tied to the fibrinolytic system. Antifibrinolytic compounds are active inhibitors of this complement system.

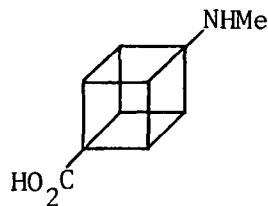
Bicyclo[2.2.2]octanes

A new potent fibrinolytic inhibitor was discovered in 1969 by scientists at Merck, Sharp and Dohme Laboratories, and has been recently reviewed in a book edited by Schor.¹⁰¹ This compound, 4-aminomethyl-



bicyclo[2.2.2]octane-1-carboxcyclic acid, was prepared on the assumption that a synthetic amino acid system with a definite rigid central nucleus would give maximum antifibrinolytic activity. The synthesis of this rigid bicyclic system was undertaken, and this approach led to the synthesis and consequent high order of activity.¹⁰² This compound was compared to known antifibrinolytic agents and was shown to be approximately sixty times more potent than ϵ -aminocaproic acid.^{103a} Baumgarten, et al^{103b} have evaluated this compound by in-vitro assay procedures.

Loeffler, et al¹⁰⁴ have reported the synthetic details, biological activities, and structure-activity relationships of various bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, bicyclo[3.2.2]nonanes and cubane derivatives as potential antifibrinolytic agents. An extensive table listing the relative activities of these fibrinolytic inhibitors is also available. Loeffler has also patented 4-(α -aminoethyl)bicyclo[2.2.2]-octane-1-carboxcyclic acid,¹⁰⁵ 4-(aminomethyl)bicyclo[2.2.2]octane-1-acetic acid,¹⁰⁶ 4-(aminomethyl)bicyclo[2.2.1]heptane-1-carboxcyclic acid,¹⁰⁷ and various aminomethylbicycloalkane-1-carboxcyclic acid derivatives.¹⁰⁸ 4-Aminomethyl-1-cubane carboxcyclic acid recently has been shown to have antifibrinolytic activities.¹⁰⁹



Anti-inflammatory Agents

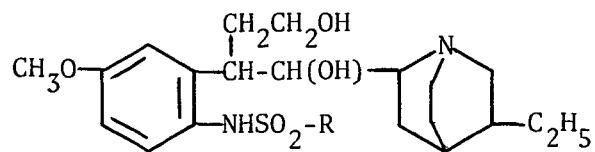
The process of inflammation involves changes in tissue in response to injury. This injury may be brought about by bacteria, trauma, chemicals, heat or other phenomena. The substance histamine and other humoral compounds are released by the damaged tissue into the surrounding fluids, resulting in the increased permeability of the capillaries. This action allows large quantities of fluid and protein, including fibrinogen, to leak into the tissues. Local extracellular edema results.

The anti-inflammatory drugs act to reduce extracellular edema. The anti-inflammatory action of these drugs is useful in treatment of rheumatic complications and acts to decrease temperature in fever.

A number of new anti-inflammatory drugs have surfaced in recent years as a result of screening using laboratory animals. These new drugs include indomethacin and flufenamic acid. In addition to the above mentioned new drugs, and the old standard used in the past, many bicyclic and cage compounds have been tested for their anti-inflammatory capacity.

Bicyclo[2.2.2]octanes

The first bicyclic system to be considered has been prepared by Maier.¹⁰⁹ Pharmacological investigations on a variety of known or novel quinuclidine compounds have been carried out. Compounds consisting of the following formula have shown that they possess a high level of

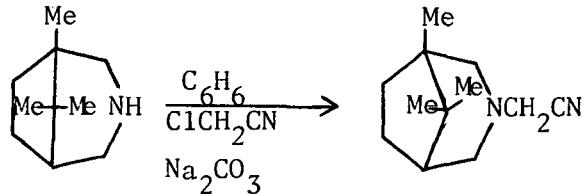


R = lower alkyl, phenyl, lower alkylphenyl

anti-inflammatory activity. Although these quinuclidine derivatives are more toxic than the known anti-inflammatory compounds, chloroquine diphosphate, the former compounds are remarkably more effective.

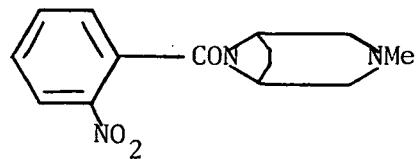
Bicyclo[3.2.1]octanes

Camphidine derivatives have been prepared that show anti-inflammatory activity.¹¹⁰ Camphidine is treated with chloroacetonitrile and sodium carbonate to give N-(cyanomethyl)camphidine,



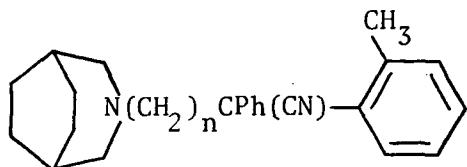
Thirteen other derivatives have also been prepared. These compounds also show antithrombic activities.

Schiatti, et.al¹¹¹ have prepared 3-methyl-8-(2-nitrobenzoyl)-3,8-diazabicyclo[3.2.1]octane which is useful in the treatment of painful inflammation of the joints and arthritic conditions.



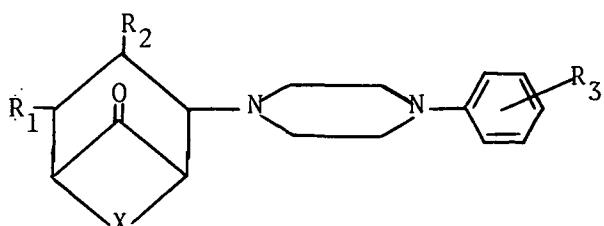
Bicyclo[3.2.2]nonanes

Complex nitriles containing the azabicycloalkane structure have been prepared by Cusic and Yonan,¹¹² The title compounds were prepared by treating an azabicycloalkanone with the appropriate derivatizing agent.



These compounds are useful as anti-inflammatory and antiulcer agents. They also inhibit the growth of bacteria and algae. Derivatives of benzophenone and benzhydrol have been shown to possess anti-inflammatory effects. A patent by Houlihan¹¹³ discloses the synthesis of various benzophenone and benzhydrol compounds. Among these numerous derivatives are the 3-(3-azabicyclo[3.2.2]non-3-ylmethyl)benzophenone and 4-(3-azabicyclo[3.2.2]non-3-ylmethyl)benzophenone hydrochloride salts. These compounds also have antidiabetic pharmacological properties.

Schutt¹¹⁴ describes the synthesis of novel aminopyran derivatives which upon heating undergo rearrangement to form bicyclo alkanone derivatives.



R_1 = H, aryl
 R_2 = H, alkyl
 R_3 = H, halogen, haloalkyl
 X = polycarbon alkylene

These compounds are used as anti-inflammatory and analgesic agents.

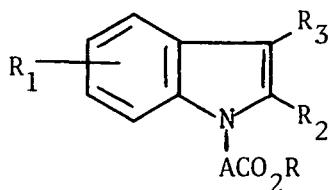
The disclosures of this patent are a continuation of U. S. Patent 3,309,370 by the same author.¹¹⁵

A series of 2-amino-bicycloheptanes, octanes, nonanes, and decanes have been prepared and are shown to be useful as anti-inflammatory agents.¹¹⁶ The compounds may be administered in the quaternary ammonium state in an admixture of pharmaceutically acceptable organic or inorganic solid or liquid carriers, given orally or parenterally.

Adamantane compounds

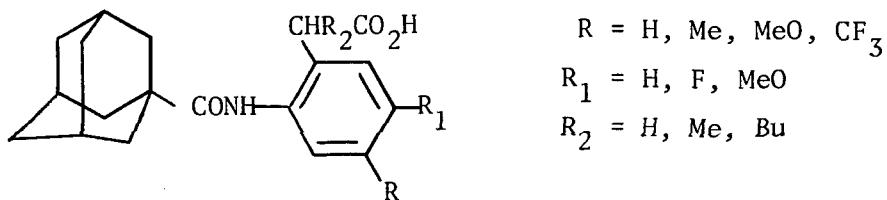
A number of adamantane derivatives have been prepared and used in anti-inflammatory preparations. The first of these compounds are the dialkylaminoalkyl and related esters of adamantane carboxyclic acids which are reported to have antibacterial, antiprotozoal, antifungal, and antialgal properties.¹¹⁷ The compounds are prepared by the reaction of an adamantane carboxyclic acid with the appropriate dialkylaminoalkyl halide. Other adamantane carboxyclic acid derivatives have been formulated by the G. D. Searle Co.¹¹⁹ and are disclosed in a French patent.

The anti-inflammatory trichloropregnadienes and esters have been prepared by Shapiro and Hershberg.¹¹⁸ Among the various 21-substituted acetates and valerates is the 21-adamantoate. Bell¹²⁰ has synthesized



the 1-(carboxyalkyl)indoles which are anti-inflammatory agents. The adamantanecarbonyl group is located at R.

Last in this series are the anti-inflammatory 0-(1-adamantane-carboxamido)-phenylacetic acid derivatives,¹²¹



These compounds were prepared from 1-adamantanecarbonyl chloride.

Antiviral Agents

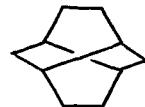
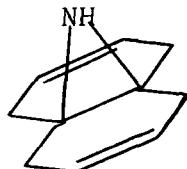
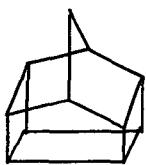
In the past, chemotherapy of viral diseases such as measles, poliomyelitis, and influenza did not exist. The larger viruses that caused trachoma and lymphogranuloma venereum responded well to antibiotics.

Recently, new developments in antiviral therapy have been realized. Idoxuridine has been used successfully in the treatment of herpetic keratitis via topical application.

The bicyclic and cage compounds that exhibit antiviral activity include: the bicyclic, adamantan and miscellaneous systems. The bicyclic systems consist of the bicyclo[2.2.2]octanes and octenes, the bicyclo [3.2.1]octanes, and the bicyclo[3.2.2]nonanes.

The adamantane types and derivatives include the most common member of this class, 1-aminoadamantane (mydantane, symmetrel, amantadine).

The miscellaneous compounds include such unusual systems as the pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecanes, the 11-azatricyclo[4.4.1.0^{1,6}]undecanes, and the tricyclo[4.4.0.0^{3,8}]decanes.

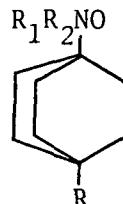
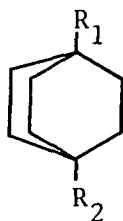


Bicyclo[2.2.2]octanes

The smallest bicyclic systems to meet the requirements of having antiviral activity are the 1-aminobicyclooct-2-enes and the bicyclooct-2-enes-1-methylamines.^{123a,b,c} These compounds show excellent ability to prevent the occurrence and growth of harmful viruses. The saturated analogue of this system has also been prepared.^{124a,b}

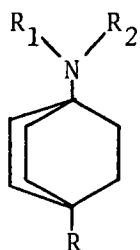
Chow¹²⁵ has prepared the bicyclo[2.2.2]octane-2-methylamine system. These compounds or their addition salts cured or prevented viral infections, especially of the A₂ strain, in warm-blooded animals.

Pig influenza has been found to be susceptible to the bicyclo[2.2.2]octane system.¹²⁶ In a patent by duPont, the following systems



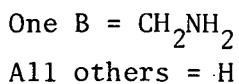
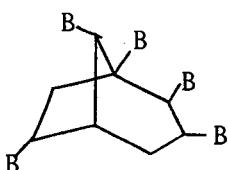
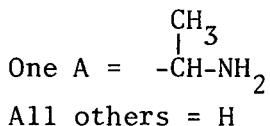
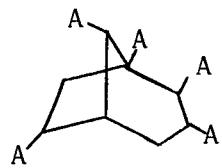
were found to have antiviral activity attended with therapeutic and prophylactic activities.

Whitney, et al¹²⁷ have synthesized various cage amines and have studied their usefulness as antiviral agents. The novel synthesis of numerous bicyclo[2.2.2]octan-1-amines and bicyclo[2.2.2]octane methyl- amines is described. It was found that the unsaturated systems were similar to their saturated counterparts, and that with the bicyclo[2.2.2]octan-1-amines optimal activity was achieved when R = methyl.



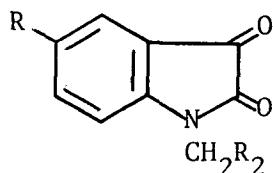
Bicyclo[3.2.1]octanes

A series of amino, aminomethyl, and α -aminoethyl bicyclo[3.2.1]-octanes that show antiviral activity have been prepared by Chow.^{128a,b}



When A or B is at the 2-position, a 40-95% increase in the survival rate of Asian flu-infected mice were observed. At the 3-position there was observed a 30-50% increase, and the 8-substituted compound showed a

45-55% increase. Varma and Nobles¹²⁹ have prepared substituted N-aminomethylisatins.



R = Br or H

R₂ = 3-azabicyclo[3.2.1]oct-3-yl or 3-azabicyclo[3.2.2]non-3-yl

These substances show a high order of activity against poliomyelitis type II, herpes simplex, measles, and parainfluenza 3 (HA-1).

Adamantane Types and Derivatives

Generally, most of the adamantane antivirals are derivatives of 1- or 2-amino adamantanes. It appears that the most active species is 1-amino adamantane and its various derivatives. The 2-amino adamantane compounds have comparable activity.

The adamantanes act by various routes. The first of these is the inhibition to penetration of the host cell by the virus. This action comes about by the coating ability of the amino adamantanes. These compounds coat the cell surface and interfere with the viral penetration thus inhibiting reproduction of the virus. This affords protection of the host cell. Other routes of inhibition include interference of multicyclic replication and inhibition of RNA synthesis. This mode of action is not virucidal, and some viruses are still able to attach themselves to the host cell wall.

The various adamantane compounds act on numerous viruses. The most common are the influenza A, A₂, C and O strains. Well-known diseases such as polio, hepatitis, Rubella, measles, and herpes simplex

infections are controlled or irradiated by the adamantane compounds.

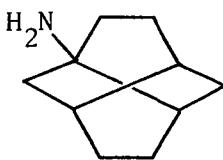
Other not-commonly-known diseases caused by viruses such as pseudorabies, and parainfluenza also succumb to the aminoadamantane drugs.

Viruses such as semiliki forest virus, tobacco mosaic, hepatic and rhino viruses are also susceptible to this antiviral action.

The literature concerning the activity, mode of action, and viral susceptibility of the adamantane antivirals is extensive. Part I of the bibliography for this chapter lists the references to antiviral compounds derived from adamantane,

Unusual Systems

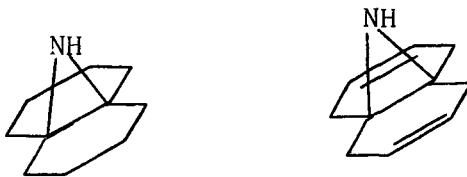
Other cage systems have been used in antiviral chemotherapy as a consequence of the widespread success of the adamantane compounds. The first of these compounds is the tricyclo[4.4.0.0^{3,8}]decan-1-ylamine system.



The antiviral actions and the intermediates used to acquire this compound are described in a patent by Deslongchamps.¹³⁰ Berthold¹³¹ has described the preparation of tricyclo[4.3.1.0^{3,8}]decane and tricyclo[4.3.0.0^{3,8}]nonane systems substituted at the 3-position with amino, aminomethyl, or α -aminoethyl groups. These compounds are prepared in a sequence of reactions from 2,6-dioxobicyclo[3.3.1]heptane-3,7-dicarboxylate. Dupont¹³² has reported the preparation of 3-aminobicyclo[4.3.1.1^{3,8}]undecane derivatives useful as antiviral agents.

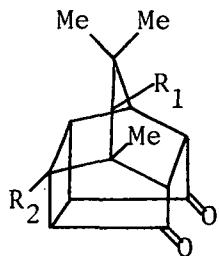
J. R. Giegy has also prepared this system by another synthetic method.¹³³ Derivatives of the 3-aminotricyclo[4.3.1.1^{3,8}]undecanes have been formulated by Cairns.¹³⁴ A typical compound is 3-N,N-dimethylamino-tricyclo[4.3.1.1^{3,8}]undecane and its hydrochloride salt.

Grunewald, et.al¹³⁵ have investigated the medicinal chemistry of [10] annulenes and related compounds. Among the compounds reported are the 11-azatricyclo[4.4.1.0^{1,6}]undecane and 11-azatricyclo[4.4.1.0^{1,6}]-undeca-3,8-diene systems. The compounds were not as effective as



1-aminoadamantane hydrochloride.

The most unusual system investigated was the trimethylpentacyclo-[5.4.0.0^{2,6}.0^{3,0}.0^{5,9}]undecan-8,11-dione derivatives.¹³⁶ The preparation of amino derivatives of this system were studied for antiviral



1. $R_1 = CO_2CH_3$, $R_2 = H$
2. $R_1 = CO_2H$, $R_2 = H$
3. $R_1 = H$, $R_2 = CO_2H$
4. $R_1 = H$, $R_2 = CO_2C_2H_5$
5. $R_1 = NH_2$, $R_2 = H$
6. $R_1 = H$, $R_2 = NH_2$

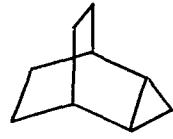
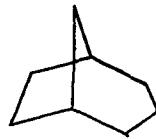
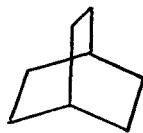
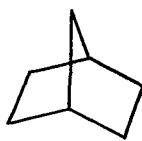
activity. Compound 5 and 6 showed no activity in vitro against influenza A (WSN), parainfluenza 1 (Sendai), and influenza A₂ (Ann Arbor).

Compounds 1 and 3 showed some activity against influenza A(WSN). Compound 5 showed superficial activity against pneumonitis.

Blood Pressure Depressants and Stimulants

The treatment of hypertension in the last few years has been revolutionized by the introduction of drugs that can lower blood pressure without intolerable side effects. These drugs act by various mechanisms, such as direct vasodilation, receptor blockage, inhibition of monoamine oxidase, ganglionic blockade, myocardial depression and increased sodium ion excretion. In most cases, therapy is directed at promoting sodium excretion. The classification of antihypertensive drugs is carried out according to their mode of action. Some of the drugs used in antihypertensive therapy are Hydralazine, Dizaoxide, Phenoxybenzamine, Ismelin, and Paragiline.

Bicyclic and tricyclic compounds are used in treatment of hypertensive states. The various classes that may be found are the bicyclo[2.2.1]heptanes, bicyclo[2.2.2]octanes, bicyclo[3.2.1]octanes, bicyclo[3.2.2]nonanes and higher classifications of polycyclic compounds such as tricyclo[3.2.2.0^{2,4}]nonanes.



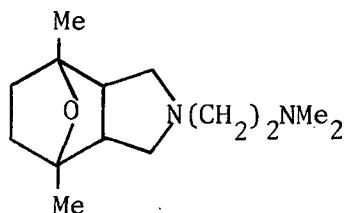
Bicyclo[2.2.2]octanes and Bicyclo[2.2.1]heptanes

Shionogi and Co. have reported the synthesis of the quaternary ammonium salts of bicyclo[2.2.2]oct-7-ene derivatives. These compounds

are reported to have excellent blood pressure lowering activity.¹³⁷

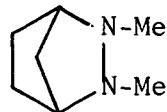
Some of the compounds prepared are acid imide derivatives such as 1'-(ω -dimethylaminopropyl)-5,7-dioxobicyclo[2.2.2]octano[2,3;3',4']-2',5'-dioxopyrrolidine,¹³⁸ various methyl iodide quaternary salts of this compound,¹³⁹ and 1'-(ω -dimethylaminopropyl)-5,7-dihydroxybicyclo[2.2.2]octano[2,3;3',4']pyrrolidine.^{140,141} This company has also manufactured 2-substituted-4,7-ethano-3a,4,7,7a-tetrahydroisoindoline-1,3-diones which also have the added ability to act as antispasmodics.¹⁴² A preparatory synthesis starting from the bicyclo[2.2.2]octane nucleus for many of the above compounds has been published by Takeda, et al.^{143,144a,b}

The 7-oxobicyclo[2.2.1]heptane-2,3-dicarboximides prepared by lithium aluminum hydride or electrolytic reduction of 3,6-endooxy-perhydrophthalimides have been reported.¹⁴⁵ These compounds, whose parent structure is Endothal (discussed in Chapter 8) have been reported to be synthesized in 80-90% yields and are converted to the acid salt or quaternary or bisquaternary salts. The isoindolines obtained in this manner are very effective in treating hypertension. Among the derivatives reported to have low toxicity is the N-dimethylaminoethyl-4,7-dimethyl-4,7-endooxyhexahydroisoindoline derivative.¹⁴⁶ A patent



has been prepared for the general synthesis of these compounds.¹⁴⁷

Endomethylene derivatives of 1,2-dimethylhexahydropyridazines showing hypotensive and ganglionic blocking activity have been prepared by Snyder.¹⁴⁸ 2,3-Dimethyl-2,3-diazabicyclo[2.2.1]heptane is a typical product.



Stern¹⁴⁹ has investigated the pharmacological action of quinuclidine and related compounds. Thioquinuclidinebromide (bicyclo[2.2.2]-1-thamiumoctane bromide), bicyclo[2.2.1]-1-thianiumheptane chloride, 1-azabicyclo[2.2.1]heptane-hydrochloride and quinuclidine hydrochloride have been reported to lower blood pressure in cats and rabbits. Bicyclo[2.2.1]-1-thianiumheptane chloride is reported to be as active as acetylcholine in lowering blood pressure.

Other bicyclo[2.2.1]heptane and bicyclo[2.2.2]octane compounds showing hypotensive properties are norbornyl derivatives of piperidyl carbamates,¹⁵⁰ camphidine compounds,¹⁵¹ α -phellandrine derivatives,¹⁵² and various basic esters of 2-norcamphanecarboxylic and bicyclo[2.2.2]octane-2-carboxycyclic acids;¹⁵³

Bicyclo[3.2.1]octanes

Grogan and Rice¹⁵⁴ have prepared a series of N-dialkylamino-3-azabicyclo[3.2.1]octane-2,4-diones. Monohydrochlorides and monomethiodides were prepared, and the quaternary salts were screened for hypotensive activity in dogs. The bisquaternary salts showed good hypoten-

sive action and a favorable therapeutic index. Other derivatives prepared demonstrating hypotensive action are the mono- and bisquaternary salts of N-dialkylamino-3-azabicyclo[3.2.1]octanes.¹⁵⁵

Systems that may also be included in the bicyclo[3.2.1]octane category that show hypotensive activity are the tropane derivatives,¹⁵⁶ the indolyl lower-alkyl tertiary amines,¹⁵⁷ and the various azabicyclo[3.2.1]octanes.¹⁵⁸

Bicyclo[3.2.2]nonanes

Laake Oy¹⁵⁹ has presented the synthesis of 3-azabicyclo[3.2.2]-nonane derivatives prepared by condensing 3-azabicyclo[3.2.2]nonane with haloamines in butanol. The quaternary salts have important blood pressure lowering abilities. The most important feature, however, is the long lasting effects. Typical representatives of these bicyclic systems are the N,N-dimethylaminoethyl-3-azabicyclo[3.2.2]nonane derivatives.¹⁶⁰

Piperidinecarboximides and some corresponding derivatives have been prepared by Kirchner.¹⁶¹ Among the derivatives prepared are the 1-carbamoyl-2-[2-(3-azabicyclo[3.2.2]nonyl)ethyl]piperidine, and 3-[2-(2-piperidyl)ethyl]-3-azabicyclo[3.2.2]nonane derivatives. These compounds were tested for hypotensive activity in the unanesthetized hypertensive rat.

Bicyclo[3.3.1]nonanes

Tucker and Lundemann¹⁶² have prepared 9-amino-9-azabicyclo[3.3.1]-nonane by treating 9-nitroso-9-azabicyclo[3.3.1]nonane with lithium aluminum hydride in diethyl ether. This compound demonstrates antihyper-



tensive and monamine oxidase inhibitory activity. Various benzamide derivatives employing 9-azabicyclo[3.3.1]nonane have also been prepared. Pharmacological tests of hypotensive activity on rats have been investigated and formulas for pellets have been given.¹⁶³

Rossi, Valvo and Butta have reported the synthesis of 3-azabicyclo[3.3.1]nonane derivatives with powerful hypotensive and ganglioplegic properties.¹⁶⁴ The compounds were prepared by replacing the amino hydrogen at position 3⁻ by a linear chain of 2-5 carbon atoms carrying at the end of this chain an amino group disubstituted with methyl or ethyl moieties.^{165,166}

The synthesis and pharmacological properties of 9-alkylamino-alkyl-substituted 3-benzyl-3,9-diazabicyclo[3.3.1]nonanes have been investigated by Nikitskaya and Gerchikova.¹⁶⁷ 3-Benzyl-9 β -diethylaminoethyl-3,9-diazabicyclo[3.3.1]nonane and various derivatives all reduced the arterial pressure in anesthetized cats by 20-50 mm for 5-10 minutes. Most derivatives also had weak central cholinolytic action and one derivative demonstrated prevention of arecoline tremors.

(Azabicycloalkyl)alkylguanidines prepared by treatment of the appropriate bicyclic amine with 5-methylisothiourea sulfate in the proper solvent have been prepared by Mull.¹⁶⁸ Representative members of this class showing antihypertensive actions are 2-(3-aza-3-bicyclo[3.3.1]-

nonyl)ethylguanidine and 2-(3,7-diaza-7-methyl-3-bicyclo[3.3.1]nonyl-ethylguanidine.

Tricyclic systems

The amidoxime O-carbamates have been demonstrated to be useful as antihypertensive agents by Henderson.¹⁶⁹ Among the derivatives prepared are tricyclo[3.2.2.0^{2,6}]non-6-yl compounds.

Blood pressure stimulants

Archer¹⁷⁰ has prepared bicyclic compounds of the tropane and granatanine series. Some of the derivatives were useful as blood pressure elevators and as stimulants to the central nervous system. Doses of 3 β -phenyltropane in dogs of 0.3 to 0.6 mg/kg raised blood pressure 40-60 mm. The methiodide salt worked equally well but the therapeutic index was lower. The 3-phenyl-2-granatenes have been shown to exert their influence on blood pressure via the central nervous system.¹⁷¹ C. F. Boehringer and Soehne have reported on the synthesis and activity of these compounds.¹⁷²

Central Nervous System Depressants and Stimulants

The central nervous system may be acted upon by various classes of drugs. Among these are the general classes of hypnotic drugs, stimulants of the convulsant type, antiepileptic drugs, narcotic analgesics, and non-narcotic analgesics.

Drugs that can produce a state of depression of the central nervous system are referred to as hypnotics. When used in small doses these drugs are active as sedatives. Hypnotics find many important uses in

medicine, such as sleeping pills, in combination with analgesics for painful states, as antidotes for stimulant or convulsant disorders. The most important members of this class are the barbituates, used as early as 1903.

A number of drugs have stimulant action on the central nervous system and when taken in sufficient doses produce convulsive states. These drugs generally stimulate respiration and combat the depressant action of barbituates. Because these stimulants have an awakening effect they are often referred to as analeptics. A majority of the analeptics act on the brain stem and some exert their action on the cerebrum. The use of central nervous system stimulants is decreasing in medical applications. The only application presently seems to be as respiratory stimulators and even this indication is somewhat debatable.

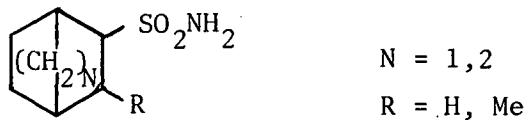
The antiepileptics are drugs that combat manifestations of paroxysmal cerebral dysrhythmia. These drugs are central nervous system depressants with a selectivity of action such that they can prevent epileptic seizures in doses that do not cause drowsiness. The antiepileptics have some undesirable side effects, but even under these conditions, a measure of protection can be afforded to approximately 80% of the epileptics. This is an outstanding achievement in the pharmacologic approach to the treatment of the disease.

The narcotic and non-narcotic analgesics have been discussed in this report under the consolidated title of Analgesics.

The various classes of bicyclic and cage compounds comprising the members of depressants and stimulants are the bicycloheptanes, octanes,

nonanes, decanes, and adamantanes. Bicycloheptanes, octanes, nonanes, and decanes are found in both classes of stimulants and depressants, but the adamantane compounds are found only in the depressants.

Daeniker¹⁷³ has prepared bicyclo[2.2.1]heptane-2-sulfonamide derivatives. These compounds are reported to have a stimulatory effect on the central nervous system when administered *inter alia*. Their stimulating or awakening effect allows them to be used as analeptics. These analeptics have the general formula:



A synthesis is described.

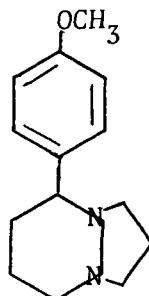
3-Arylquinuclidines and selected derivatives have been reported to have a stimulatory effect on the central nervous system.¹⁷⁴ They also have an excitatory effect on respiration. The 3-arylquinuclidines are prepared by treating 3-quinuclidone with an arylmetallic compound, dehydrated, and then hydrogenated to give the product.

Other bicyclo[2.2.2]octanes shown to have central nervous system stimulant properties are the 2-(3,4-disubstituted phenyl)-3-amino-bicyclo[2.2.2]octan-2-ols,¹⁷⁵ and the N-cycloalkyl and N-(cycloalken-1-yl)azabicyclooctanes.¹⁷⁶

Some of the commonly used central nervous system stimulants are known to have caffeine-like¹⁷⁷ activities. Others may exhibit alleviation of mental depression and may have veterinary uses.^{178,179} The N-cycloalkylazabicyclo[3.2.2.]nonane derivatives have been shown to have

inhibitory pseudocholinesterase, urinary secretion and anti-inflammatory activities.¹⁸⁰

Houlihan¹⁸¹ has synthesized diazabicyclononanes of the general



formula which have central nervous system stimulant properties. Also prepared were the 2-phenyl and 2-(2-chlorophenyl) derivative.

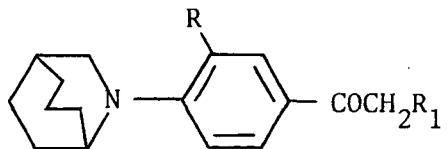
Central nervous system depressants

The N-aralkyl camphidines have been investigated for their central nervous system depressant activity by Hermanson.¹⁸² He found that two N-aralkyl-5-substituted camphidine salts had a sedative effect on the central nervous system. The toxicology and other effects were also investigated. The chemical structure and sedative effect were studied in order to determine structure-activity correlations. When the camphidine ring was substituted with other heterocyclic structures, no sedative activity was observed. A chlorine atom substituted at the 5-position of the camphidine ring lowered the effectiveness of the drug, while chlorine, nitrite, methyl, and methoxy substitution on the benzyl ring enhanced the effect. Other camphidines have demonstrated depressor activities on the central nervous system.¹⁸³

1-Azabicyclo[2.2.2]octanes have been shown to possess central nervous system depressor activities. Compounds of this type are 2,3-

heterocyclic fused quinuclidines¹⁸⁴ and various bicyclo[2.2.2]oct-5-ene-bis (2,3-dicarboximide) compounds.¹⁸⁵

3-Azabicyclo[3.2.2]nonanes have demonstrated central nervous system properties.¹⁸⁶ These compounds have the general structure:



Formulation for oral doses may also be encountered in this patent.

The last of the bicyclic compounds to show central nervous system activity are the bicyclic glutarimides, bicyclic barbituric acid, and bicyclic oxazolidinediones.¹⁸⁷ The synthesis of these compounds was conducted in order to study the possibility of the existence of a unified anticonvulsant receptor site.

Szinai and Lunn¹⁸⁸ have prepared adamantane derivatives that show central nervous system depressant action. Some of the derivatives prepared were the 1-acetyl adamantane and 1,2-dimethyl adamantane[2,1-b]-pyrrolidine. About 30 derivatives have been prepared. A series of adamantane compounds having central nervous system and antihistaminic activity have been prepared by Bernstein.¹⁸⁹ These compounds are useful in the treatment of allergies and Parkinsonism. 1-Substituted amino-adamantanes have also demonstrated central nervous system depressant activity.¹⁹⁰

Contraceptives

In 1959, the first report of successful inhibition of ovulation by orally administered norethynodrel-mestranol compounds appeared. By

1966, more than seven million women were taking oral contraceptives although the use of such contraceptives had some unpredictable side-effects. However, the results indicate that these drugs are the most effective means of preventing pregnancy.

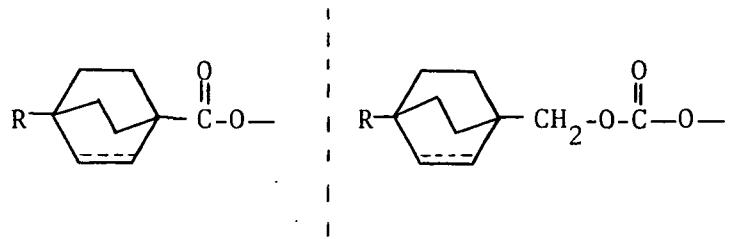
There are three types of contraceptive formulations:

- (1) Progestogen-estrogen combinations; (2) Sequential estrogen-progestogen; and (3) Low-dosage progestogens.

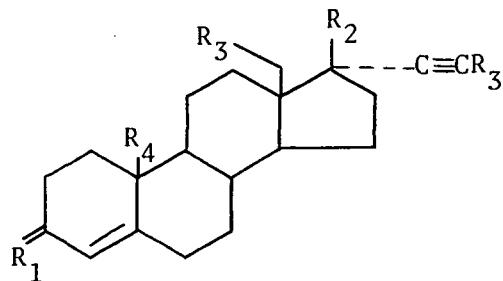
Most of the bicyclic and cage compounds incorporated into contraceptives are bicyclo[2.2.2]octane and adamantane derivatives. The bicyclo[2.2.2]octanes are either androstane steroid esters or estrogenic steroids. The adamantane compounds in themselves have pronounced antifertility and therefore contraceptive activities.

Bicyclo[2.2.2]octanes

Cross and Fried¹⁹¹ have prepared the bicyclo[2.2.2]octane-1-carboxylate and bicyclo[2.2.2]octane-1-methylenecarbonate esters of androstane and 19-norandrostane steroids. These esters have long-acting antifertility progestational activities, and have the general formula

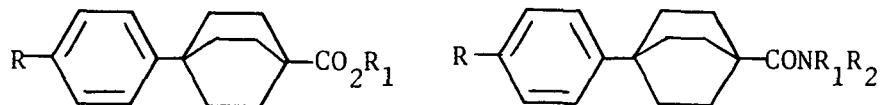


The dotted line represents a possible double bond. The steroid nucleus to which these bicyclooctanes are attached have the general formula

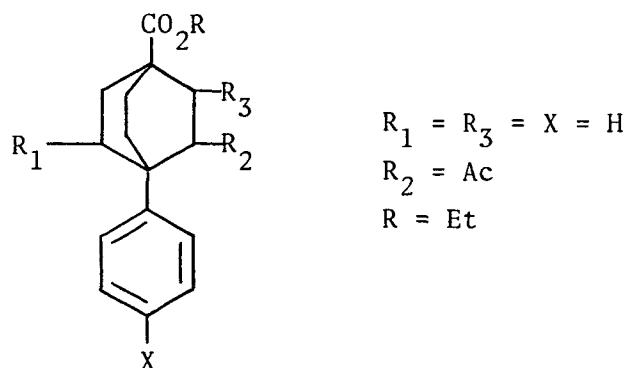


and the bicyclic moieties are attached at either R_1 or R_2 . The bicyclo[2.2.2]octane-1-carboxylate and bicyclo[2.2.2]octane-1-methylene-carbonate may also be attached to an estrogenic steroid via the ester linkage.¹⁹²

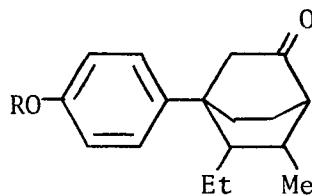
Aldrich and Herrmann^{193a} have prepared a series of 4-phenylbicyclo[2.2.2]octane derivatives that show contraceptive actions.^{193b} These compounds have the general formula



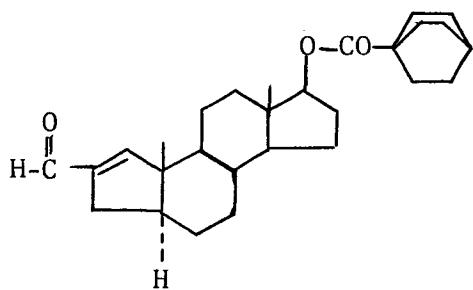
and it was found that when applied in amounts of 0.01 to 5 mg/kg could prevent pregnancies in rats.^{193c} Another similar system with the general formula seen below and prepared by Gregory and Lee represents compounds that may be useful as contraceptives.¹⁹⁴ Karmas¹⁹⁵ has



reported that the 2-methyl-3-ethyl-4-(substituted-phenyl)cyclohexane carboxyclic acid derivatives possess useful anti-littering properties in animals. These compounds have the following formula:



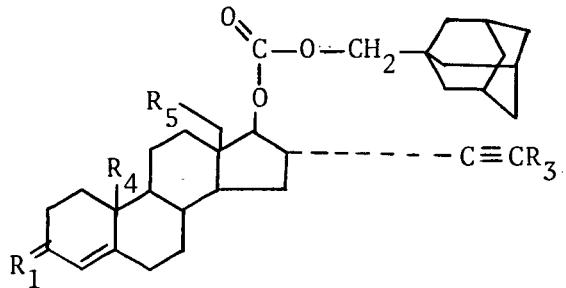
Selected 2-formyl- and 2 α -(cyanoamidino)-A-nor-5 α -androstane derivatives have demonstrated antifertility properties.¹⁹⁶ The 2-formyl-A-nor-5 α -androst-1-en-17 α -olbicyclo[2.2.2]-octane-1-carboxylate derivatives has been prepared. This compound has the formula



and is prepared with bicyclo[2.2.2]octane-1-carboxycyclic acid chloride and 2-formyl-A-nor-5 α -androst-1-en-17 β -ol.

Adamantane derivatives

Adamantane derivatives of androstane and estrogenic steroids have been prepared. Cross and Fried¹⁹¹ in preparation of their androstane and 19-norandrostane steroidal esters prepared the tricyclo[3.3.1.1^{1,5}]-decan-1-methylenecarbonate(adamantane-1-methylene carbonate)derivative. This compound is prepared from adamantane-1-carboxycyclic acid and the corresponding androstane alcohol. The synthetic preparation of the

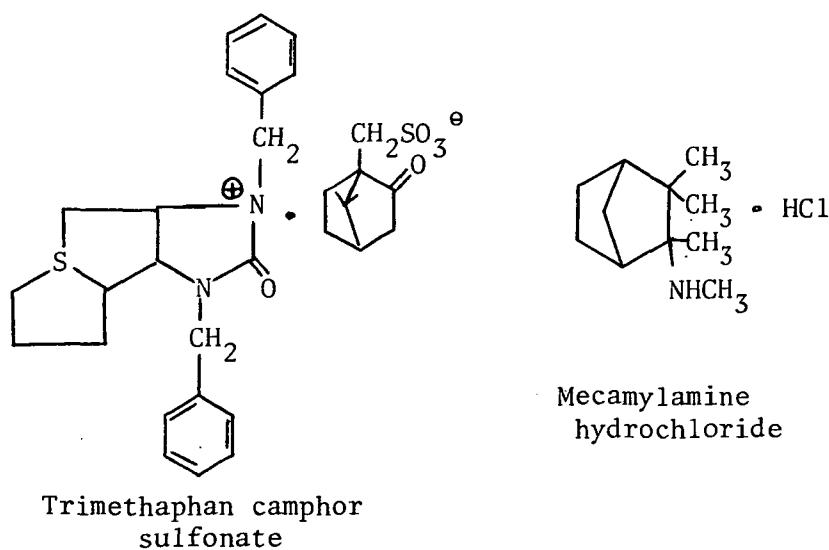


adamantane derivative in the estrogenic steroid series is very similar.¹⁹² Schribner¹⁹⁶ describes the preparation and properties of the 2-formyl-A-nor-5 α -androst-1-en-17 β -ol adamantane-1'-carboxylate. This compound is prepared from adamantane-1-carboxyclic acid chloride and 2-formyl-A-nor-5 α -androst-1-en-17 β -ol and demonstrates antifertility properties.

Other adamantane-compounds that show antifertility or antizygotic activity have been prepared. These compounds are adamantane(substituted phenyl),¹⁹⁷ 2,3-dialkyl-4-arylhexenemethanols,¹⁹⁸ and esters of 2-methyl-3-ethyl-4-phenylcyclohexanecarboxycyclic acids.¹⁹⁹

Ganglionic Blocking Drugs

The development of ganglionic blocking agents began with the discovery that nicotine could block ganglionic transmission. Langley made extensive use of nicotine as a local application for charting sympathetic ganglia in the cat. Tetraethylammonium salts were also known for years to block the effect of ganglionic stimulants, and in 1946, the mode of action on mammalian circulation was thoroughly investigated.²⁰⁰ From the results of this investigation it was suggested that ganglionic transmission may be blocked in a selective manner. Interest in hypertensive diseases and vasospastic disorders initiated the expansion of the investigations of ganglionic blocking activity. From this a variety of ganglionic blocking agents were developed. Some of the most common compounds are hexamethonium, pentolinium chlorisondamine, and trimethaphan camphor sulfonate. The newest members of this class are mecamylamine and pempidine. Trimethaphan camphor sulfonate and mecamylamine are bicyclic compound derivatives.



The majority of ganglionic blocking drugs are quaternary ammonium compounds and are used principally for decreasing the action of the sympathetic division of the autonomic nervous system on circulation. Numerous side effects may be noticed due to hinderance of parasympathetic ganglionic transmission.

The bicyclic and cage compounds employed in ganglionic blocking agents are bicyclo[2.2.1]heptanes, bicyclo[3.2.1]octanes, bicyclo[3.3.1]-nonanes, and the bicyclo[4.2.1]nonane derivatives. Some of these compounds are congeners of mecamylamine and pempidine, and most are quaternary ammonium compounds, all possessing the ganglionic blocking ability via depolarization inhibition of acetylcholine.

The ganglionic blocking activity of aminobicyclo[2.2.1]heptanes have been investigated by Corne, Lee, and Wratt.²⁰¹ The structure-activity relationships for ganglionic blocking action in lower homologues of mecamylamine are discussed. Activities in larger rings were found to be similar and successive introduction of C-Me surrounding the nitrogen atom resulted in an increase in ganglionic blockade and duration of action. When compared to hexamethonium, these compounds were found to be comparable in action. Acute oral and intravenous toxicities and requirements for strong ganglionic blocking action are also discussed.²⁰²

New bisquaternary compounds have been derived from 3,5-ethylene-piperidine and its derivatives, most notably camphidine, by quaternization with alkyl or aralkyl salts of inorganic or organic acids.²⁰³ Numerous quaternary compounds of 1-(3-dimethylamino propyl)-3,4,4-

trimethyl-3,5-ethylenepiperidine have been prepared. N-substituted chlorinated camphidine derivatives containing NH_4^+ groups in the side chain have been shown to have strong ganglionic blocking properties.^{204a} Pharmacologic properties have also been reported.^{204b}

Tertiary-amino substituted compounds of the tropane and granatane series demonstrating ganglionic blocking actions have been investigated.²⁰⁵ Pharmacologic investigation via response in dogs and nictitating membranes in cats has demonstrated that these compounds have ganglionic blocking effects. The quaternary ammonium salts of these compounds are highly effective.

The pharmacological properties of 3-azabicyclo[3.3.1]nonane have been investigated by Tommasini and Passerini.²⁰⁶ The compounds specifically investigated were the derivatives of 3-isogranatanine. The methyl derivative was found to be active due to its ganglionic blocking activity. A derivative of 9-methyl-3,9-diazabicyclo[3.3.1]nonane has been investigated for its pharmacologic properties by Nikitskaya, Usovskaya and Rubtsor.²⁰⁷ 3-(3-Dimethylaminopropinyl)-9-methyl-3,9-diazabicyclo[3.3.1]nonane and similar tetramethylene derivatives had strong curare activity similar to that of decamethonium. Curare-like actions on impulse conduction in cats are found in a similar derivative, nobutane(1,4-bis(9-methyl-3,9-diazabicyclo[3.3.1]nonano-3)butane).²⁰⁸ The pentamethylene and hexamethylene derivatives had similar activity but were weaker.

4,9-Diazabicyclo[4.2.1]nonane derivatives have been shown to have ganglionic blocking actions and demonstrate serotonin antagonism.²⁰⁹ Representative members of these compounds are 4-benzhydryl-9-methyl-4,9-diazabicyclo[4.2.1]nonane and 4-(9-fluorenyl)-9-methyl-4,9-diazabicyclo[4.2.1]nonane.

Hypoglycemic Agents

The introduction of hypoglycemic sulfonylurea compounds greatly enhanced the management of diabetes. In 1942, Laubatieres^{210,211} observed that certain sulfonamides produced symptoms of hypoglycemia. Subsequent investigations in other laboratories established that certain sulfonylureas can produce hypoglycemia in certain animals. The most commonly used sulfonylureas used today are tolbutamide, chlorpropamide, acetohexamide, and tolazamide.

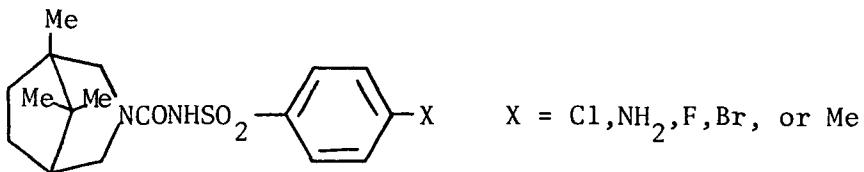
Most of the bicyclic and cage compounds are sulfonyl or sulfonyl semicarbazide derivatives. They are composed of the classes of bicycloheptane, bicyclooctane, and bicyclononane compounds, and the adamantanone and tricyclo[4.3.1.1^{3,8}]undecane derivatives.

Bicyclo[2.2.1]heptanes and Bicyclo[2.2.2]octanes

Bicyclo[2.2.1]heptane compounds possessing antidiabetic actions have been prepared by Winter, et.al.²¹² Among the sulfonylureas prepared was the bicyclo[2.2.1]hept-2-yl derivative. Nortricyclamine phenyl-sulfonyl urea compounds, considered as a class of bicyclo[2.2.1]heptanes, have also demonstrated blood sugar level reduction ability.²¹³ Nontoxic benzenesulfonylureas have demonstrated hypoglycemic properties.^{214a,b} Other compounds have been prepared by Dietrich²¹⁵ and J. R. Giegy, A.-G.²¹⁶ The quinuclidine derivatives have also shown antidiabetic and hypoglycemic properties.^{217,218}

Bicyclo[3.2.1]octanes and Bicyclo[3.2.2]nonanes

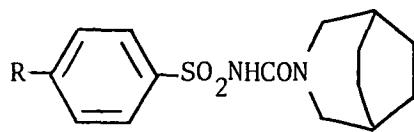
Hypoglycemic (benzenesulfonamidocarbonyl) camphidines with the general formula



have been prepared by Carron, et al.²¹⁹ The chlorine derivative decreased rat glycemia after an oral dose of 125 to 250 mg/kg. These compounds also had peripheral spasmolytic and blood pressure effects.

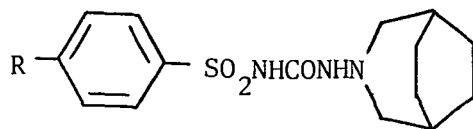
A new synthesis of nortropane (8-azabicyclo[3.2.1]octane) and the acid addition salts of these compounds has been reported.²²⁰ The products are intermediates in the preparation of orally active anti-diabetics and diuretics. These compounds are prepared from azabicyclooctanes in which the nitrogen atom is substituted with a methyl group which is then substituted with a hydrogen atom.

The preparation of 3-azabicyclo[3.2.2]nonane phenylsufonylurea derivatives has been described.²²¹ These compounds and their addition salts are useful as blood sugar-reducing agents. A number of derivatives with the general formula



$\text{R} = \text{H, halogen, alkyl, alkoxy, alkylthio, or acyl}$

have been formulated. A very similar derivative has been shown



to have pronounced hypoglycemic effects and low toxicity.²²² These compounds find use in the management of diabetes mellitus.²²³

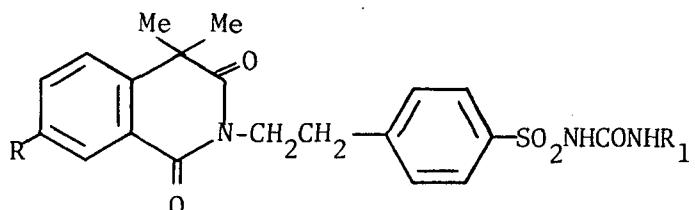
Bicyclo[3.3.1]nonanes

Sandoz, Ltd, has prepared antidiabetic compounds useful in treating diabetes mellitus via reducing the effects of this condition.²²⁴

These compounds are derivatives of 9-azabicyclo[3.3.1]nonanes and have prolonged effects.^{225,226} Other compounds found useful in the treatment of diabetes are phenylsulfonylsemicarbazides of the N-amino-granatane (9-azabicyclo[3.3.1]nonane)²²⁷ and 3-azabicyclo[3.3.1]nonane²²⁸ class.

Adamantane Derivatives

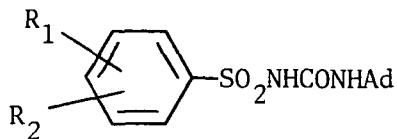
Pharmacological isoquinoline derivatives having the formula



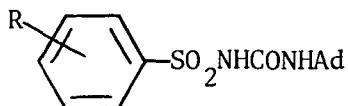
R = H, Br, Cl
R₁ = 1-adamantyl

have demonstrated blood sugar lowering activities.²²⁹ These compounds are prepared by the condensation of sulfonamides with the appropriate

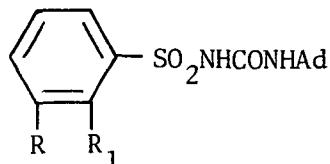
adamantyl isocyanate. Dietrich has prepared various N-adamantyl-N¹-arylsulfonylureas having antidiabetical properties.^{230a,b,c} These compounds have the general structures



R_1 = halogen, CF_3 , alkyl, alkoxy, alkylthio
 R_2 = halogen, CF_3 , alkyl, alkoxy, satd alkyl group



R = CF_3 , low alkenyl, alkanoyl, Ar



R_1 = halogen, H, alkyl, alkoxy, alkylthio
Ad = adamantane

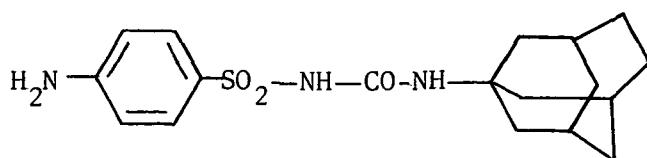
and may be prepared by the reaction of 1-aminoadamantane, the corresponding arylsulfonyl isocyanate, or an arylsulfonyl urethane or urea.

When $R=CF_3$, acyl, alkenyl, or aryl, these compounds show high hypoglycemic activity and low toxicity in warm-blooded animals.^{231,232}

Gerzon²³³ has also prepared a series of N-(substituted)-phenylsulfonyl-N¹-1-adamantylureas.

Tricyclo[4.3.1.1^{3,8}]undecanes and Miscellaneous systems.

It has been observed that N'-tricyclo[4.3.1.1^{3,8}]undec-3-yl-N-p-aminobenzene-sulfonylureas of the formula



possess strong hypoglycemic action when given orally or parenterally even in low dosages.²³⁴ These compounds have hypoglycemic action much greater than the known pharmaceutically accepted antidiabetical compounds containing alkyl substituents of 3 to 4 carbon atoms at the phenyl nucleus. Consequently, the therapeutic index is much more favorable than the existing oral antidiabetics. The derivatives described here are prepared by reacting tricyclo[4.3.1.1^{3,8}]undecane-3-amine with an arylsulfonyl isocyanate. A Netherlands patent covers other N-aryl-sulfonyl-N'-tricyclo[4.3.1.1^{3,8}]-3-undecylurea derivatives as antidiabetical compounds.²³⁵

Miscellaneous hypoglycemic compounds of bicyclo[3.1.1]heptane, bicyclo[3.2.1]octane, and bicyclo[3.3.1]nonanes have been prepared by Tucker, et al.²³⁶ These compounds show hypoglycemic activity in rats, and also demonstrate low oral toxicity. Weber, et al²³⁷ have also prepared bicyclo[2.2.2]octane and bicyclo[3.2.1]octane hypoglycemic (phenylsulfonyl)ureas.

Local Anesthetics

Local anesthetics produce transient and reversible loss of sensation in a circumscribed area of the body by interfering with nervous conduction. In 1884 the drug cocaine was introduced by Koller. This drug was used as a topical anesthetic in ophthalmology.

In 1904 procaine was introduced by Einhorn. Procaine could be injected and was the first local anesthetic in which this could be safely done. Procaine was used exclusively and widely until lidocaine came to be known. Lidocaine is now considered the drug of choice for local anesthesia. Other important local anesthetics are tetracaine,

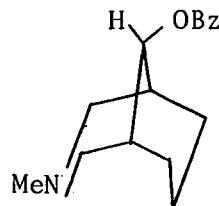
mepivacaine, prilocaine, and bupivacaine. All of the local anesthetics are either esters or amides, and are different in their toxicity, metabolism, onset, and duration of action.

Electrophysiologic studies demonstrate that the local anesthetics interfere with the depolarization phase of the action potential. As a consequence, when a nerve cell is excited, the cell does not depolarize sufficiently and thus a propagated action potential is blocked.

Represented in the class of local anesthetics are the bicyclo[3.2.1]octanes, bicyclo[3.3.1]nonanes, bicyclo[4.3.1]decanes and adamantane derivatives.

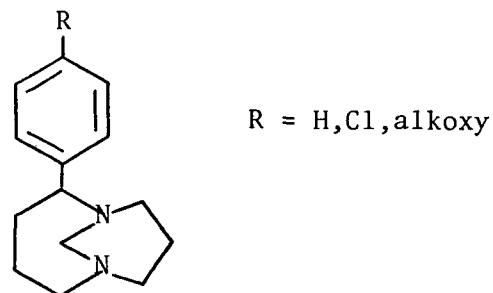
N^+ -[N -(monocarboxycyclic aryl)carbanoyl]-lower alkyl amines have been reported to have local anesthetic properties.²³⁸ In particular the nortropane (8-azabicyclo[3.2.1]octane) derivatives are prepared by adding N -(2,6-dimethylphenyl)carbamoylmethyl chloride to nortropane. Other bicyclo[3.2.1]octane derivatives showing intravenous local anesthetic action are (bicyclo-octenyl)-alkyl maleic acid derivatives.²³⁹ These compounds also exhibit soporific actions.

Ohri, et al²⁴⁰ have prepared twenty 3-azabicyclo[3.3.1]nonane derivatives and have examined them for analgesic activity. In their findings they report that the 3-methyl-9-benzyloxy-3-azabicyclo[3.3.1]nonane derivative



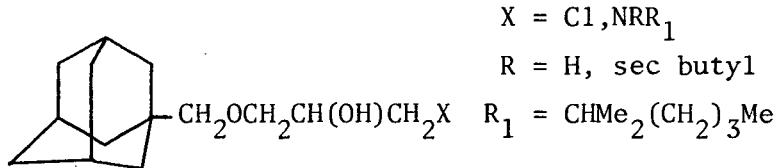
exhibited local anesthetic activity comparable to that of procaine-hydrochloride.²⁴¹

Houlihan²⁴² has demonstrated that diazacycloalkanes of the general formula



have local anesthetic activity by actions via the central nervous system.

Adamantane derivatives that have local anesthetic activity and that block adrenergic response are reported to be prepared in good yield.²⁴³ These 1-(adamantylmethoxy)-2-hydroxy-3-propylamines have the general formula



Parkinsonism Drugs

With the discovery of L-dopa, the pharmacology of Parkinson's Disease has been greatly revolutionized. In the past, the treatment of this disabling condition has been carried out with (1) the belladonna alkaloids and congeners, (2) antihistamines, (3) anticholinergic and antihistimimic combinations, and (4) dextroamphetamine for the treatment

of some conditions of postencephalic parkinsonism.

Parkinson's Disease is characterized by tremor, rigidity, and akinesia and other paralysis syndromes and postencephalic conditions. This disease may also be caused by drugs. The treatment of Parkinson's Disease was described more than a hundred years ago by the administration of belladonna alkaloids.

Some of the drugs used to treat Parkinson's Disease are trihexyl-phenidyl hydrochloride, diphenhydramine hydrochlorides, benztrapine mesitylate, and orphenadrine hydrochloride.

Bicyclo[3.3.1]nonane and adamantane derivatives have found use in the treatment of Parkinson's Disease. These compounds act in a similar manner to the previously described drugs.

The pharmacological properties of 6,6,9-trimethyl-1-azabicyclo-[3.3.1]non-3- β -yl α ,aa,-di(-2-thienyl)glycolate hydrochloride monohydrate, a new anti-Parkinsonian agent, has been studied by Nose, et al.²⁴⁴ This compound may be useful in the treatment of Parkinson's Disease and shows no major undesirable side effects. When studied, this drug has pronounced anti-acetylcholine, anti-tremorine-induced tremor, anti-physostigmine-induced death, anti-haloperidol-induced Parkinsonism and anti-EEG arousal activities. A study has also been conducted on the metabolic fate of this drug.²⁴⁵ 2-(3-Azabicyclo[3.3.1]nonyl)ethyl esters of α -phenyl- α -isopropylglycolic acid have demonstrated activity in treating Parkinson's Disease.²⁴⁶

Intravenous doses of amantadine hydrochloride as small as 8.0×10^{-2} milligrams/kilogram may release dopamine and other catecholamines from neuronal sites in dogs.²⁴⁷ Selective anticholinergic

effects could not be demonstrated in animal tests. Amantadine was concluded to be 1/209,000 as potent as atropine in antagonizing contractions of guinea pig ileum treated with acetylcholine. Amantadine has also demonstrated antagonization of chlorperazine²⁴⁸ and harmaline²⁴⁹ induced dreams.

Adamantane derivatives that demonstrated dopamine on catecol amine release have been reported by Shromberg²⁵⁰ and Scaffon.²⁵¹

Pharmaceutical Applications

Pharmaceutical bicyclic and cage compounds found in the literature may be divided into many classes, such as pharmaceutically acceptable salts, intermediates in the preparation of compounds useful in pharmacy and agriculture, and in the production of drugs. These compounds are mentioned in the individual reports, but no specific medicinal action is listed. For this reason, compounds with "pharmaceutical" activity are listed in Part II of the bibliography for this chapter.

Sedatives

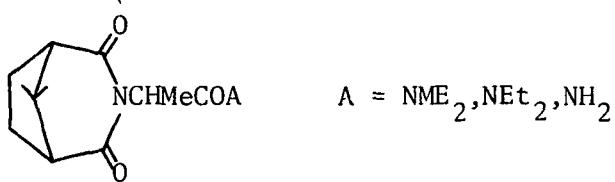
Hypnotics, when used in small doses, are referred to as sedatives. Hypnotics produce a state of depression of the central nervous system resembling normal sleep. The sedatives produce a state of drowsiness. When used in large doses, sedative-hypnotics can produce anesthesia, coma, and death.

The most important sedative-hypnotics are the barbiturates. When used properly these drugs are safe and highly effective. Although they are habit-forming and may lead to addiction, these compounds are not necessarily inferior to the new sedative-hypnotics. The newer drugs are piperidinediones such as glutethimide and methyprylon. Besides

the barbiturates and piperidinediones are the carbamates, bromides, alcohols, and paraldehyde.

The bicyclic and cage compounds finding use as sedatives are the bicyclo[3.2.1]octane, bicyclo[3.3.1]nonane and adamantane systems. Many of these compounds are similar to barbituric acid or piperidine-dione.

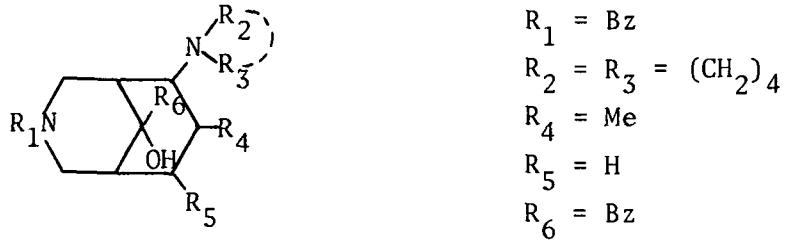
Takahashi, Fujimura, and Hamajima²⁵² have formulated 1,8,8-dimethyl-3-azabicyclo[3.2.1]nona-2,4,-dione derivatives that show sedative action. These compounds have the general formula



and are prepared from 1,8,8-trimethyl-3-azabicyclo[3.2.1]octane (camphorimide), α -bromopropynylmethylamine and sodium hydroxide.

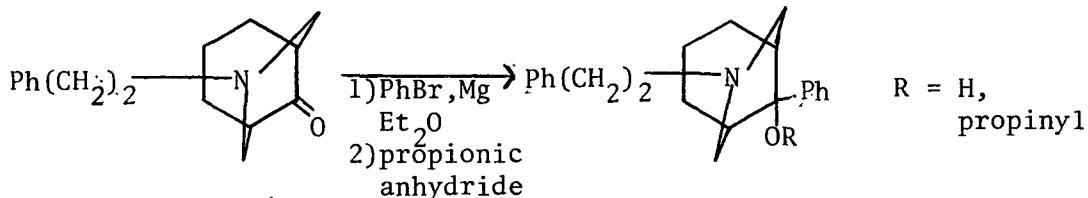
Derivatives have also been prepared with N,N-dimethylchloracetamide. ²⁵³

3-Azabicyclo[3.3.1]nonane compounds of the general formula

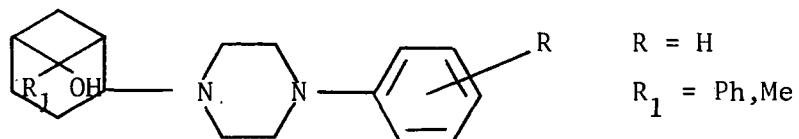


have been prepared by Nakanishi, Arimura, and Muro.^{254a,b} These compounds demonstrate useful sedative and analgesic action. A number of derivatives all varying at R_1 to R_6 have been synthesized. A similarly structured compound has been prepared from 3-phenethyl-9-

oxo-3-azabicyclo[3.3.1]nonane via the Greignard reaction with bromobenzene.



The products are sedatives.²⁵⁵ 2-(4-Arylpiperazine)bicyclo[3.3.1]nona-9-ol derivatives have been reported to have sedative action.²⁵⁶ These compounds have the formula



and the free amine and hydrochlorides have long-term sedative effects. Administration of the drug to mice caused a decrease of spontaneous motor activity and loss of coordinated motor activity.

The adamantane group in sedative preparation has been reported by Gerzon, et al.²⁵⁷ 3,5,7-Trimethyladamantane-1-carboxamide was prepared in 90-95% yield. The sedative activity in mice has also been investigated, and structure-activity relationships are contrasted with previously described adamantane containing agents.

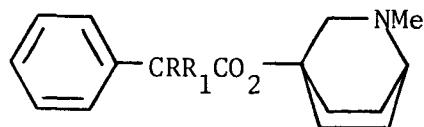
Spasmolytics

The spasmolytics or antispasmodics are drugs that abolish spasms that occur in the involuntary muscles innervated by the central nervous system. The abolition of muscarinic effects prevents spasm of involuntary muscle and the drugs causing this are called neurotropic antispasmodics. Atropine is an example of this type of drug. Furthermore, some antispasmodics act directly on the muscle cells regardless of innervation and these drugs are called muscarotrophic antispasmodics. Papaverine is an example.

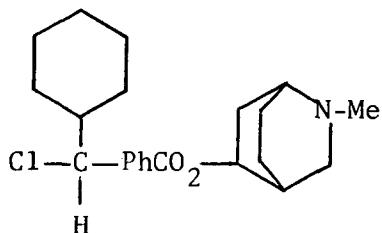
The bicyclic compounds found in use as spasmolytics are bicyclo[2.2.1]heptanes, bicyclo[2.2.2]octanes, and bicyclo[3.2.1]octanes. Many of the spasmolytics are esters of quinuclidines and bicyclic alcohols. Some are amine derivatives.

Klavehn²⁵⁸ has prepared basic acid esters of bicyclo[2.2.1]heptane compounds useful as spasmolytics. Among the compounds prepared are [2-hydroxybicyclo[2.2.2]heptyl]-2-phenylacetic acid and various hydrochloride and methosulfate salts.

Spasmolytic 5- or 6-phenylacetoxy-2-methyl-2-azabicyclo[2.2.2]-octanes have been prepared by Bernardi et al.²⁵⁹ These compounds with the following structure



are reported to have high antispastic activities at low toxicity and are prepared by esterification in the presence of an amine. A similar type of compound



prepared by the same researchers exhibited improved in-vitro and in-vivo antispastic activity. The compounds prepared were the hydrochloride and methyl iodide salts.²⁶⁰

Basic bicyclic esters prepared by Sternbach have been demonstrated to have antispastic actions.^{261,262} Ester derivatives of the 1-azabicyclo[2.2.2]octan-3-ol series are useful as spasmolytics. Esters of bicyclic amino alcohols have been tested for spasmolytic actions with isolated intestine.²⁶³ These esters demonstrated activity similar to atropine while others were considerably weaker.

Spasmolytic 3,8-disubstituted-3,8-diazabicyclo[3.2.1]octanes with spasmolytic action have been prepared by Kirchner.²⁶⁴ A large number

of derivatives have been prepared and some show local anesthetic activity also.

Steroid Compounds

The various steroid compounds investigated in this report are of four kinds: (1) testosterone derivatives, (2) pregnane derivatives, (3) estrane derivatives and (4) androstane derivatives.

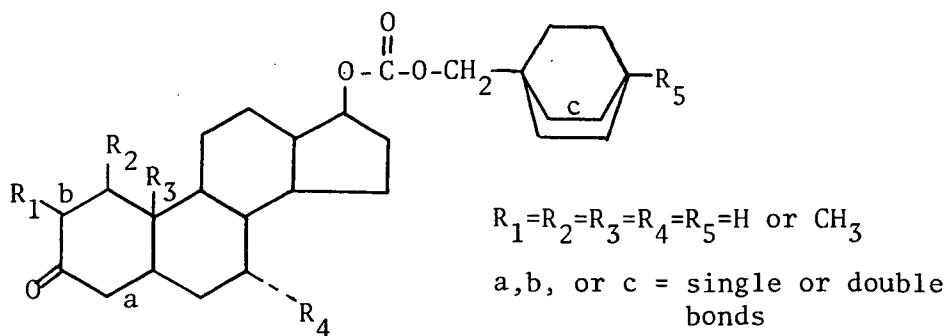
Testosterone is an androgen and is the principal testicular hormone. The esterification of testosterone gives compounds with certain advantages such as superior oral or anal absorption and longer lasting effects.

Testosterone is the hormone responsible for the development and maintenance of male secondary sex characteristics. Testosterone has a protein anabolic effect; it can produce a positive nitrogen, potassium, phosphorus, and sodium balance. This compound also demonstrates myotropic and androgenic effects.

The bicyclic and cage compounds that have found use as functional groups of a steroid nucleus are the bicyclo[2,2,2]octane and adamantine compounds. These derivatized steroid compounds show myotropic, androgenic, corticoid, and hormonal and antihormonal activities.

Bicyclo[2,2,2]octanes

Boswell²⁶⁵ has introduced the bicyclo[2,2,2]octane-1'-methyl and 4'-methylbicyclo[2,2,2]octane-1'-methyl carbonates of variously substituted testosterones and 19-nortestosterones, as represented by the following formula:



These compounds may be prepared by reaction of the steroidal chloro- or fluoroformate with the bicyclooctylmethyl alcohol,²⁶⁶ or by reaction of the steroidal alcohol with the bicyclooctylmethyl chloroformate.

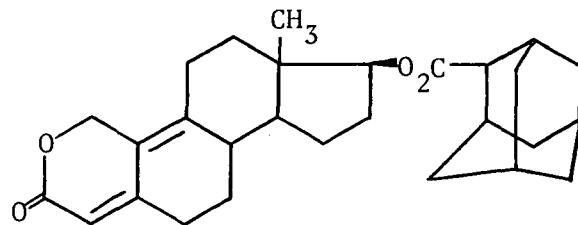
Cross and Fried²⁶⁷ have prepared a bicyclo[2.2.2]octane-1-carboxylate and bicyclo[2.2.2]octane-1-methylenecarbonate esters of Δ^4 pregnane corticoid steroids. These compounds demonstrate long acting corticoid and antiinflammatory activity.

Adamantane compounds

Rapala²⁶⁸ has prepared esters of cortico steroids. The esterification of cortico steroids with 1-adamantoic acid anhydride, the mixed anhydride of 1-adamantoic acid and trifluoroacetic acid, or 1-adamantoic acid chloride was carried out. Among the compounds prepared are fluoro-andrenolone 21-(1-adamantoate) and prednisolone 21-(1-adamantoate).

Rapala has also prepared new esters of 3-methoxyestradiol with 1-adamantanecarboxylate,^{269a,b,c} showing antiandrogenic effects, testosterone esters²⁷⁰ having very high myotropic-androgenic ratios with antiestrogenic activity, and 19-nortestosterone-17 β -adamantoate esters²⁷¹ possessing a profound and unique anabolic potency with high myotropic activity.

Various steroidal esters have been shown to demonstrate anabolic, androgenic, or hormonal and antihormonal activities. Those compounds that are anabolic-androgenics are 17-acyloxy-2-oxaestra-4,9-dien-3-ones and adamantane derivatives²⁷² of the general formula



The 1-adamantyl and 1-adamantylmethyl carbonates of testosterone²⁷³ and 7 α -difluoromethylandrosten-3-ones²⁷⁴ show these effects also.

Compounds that show activities besides anabolic actions are the 1-halomethyl-5 α -androstanes and androst-1-enes²⁷⁵ and various adamantoate esters of 13 β -alkylgon-4-en-3-ols.²⁷⁶

A number of syntheses involving the use of adamantane derivatives have been reported. Among these are corticosteroid 21-(1-adamantoates),²⁷⁷ esters of 17 α -ethynyl-13 β -ethylgonene-3,17 β -diols,²⁷⁸ 14 β -estr-4-enes,²⁷⁹ and 6-halo-9 β ,10 α -androstadienes and trienes.²⁸⁰

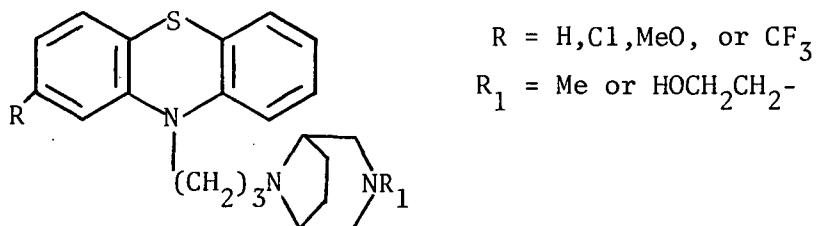
Tranquilizers

Antipsychotic and antianxiety drugs are substituted newer terms for the major and minor tranquilizers, respectively. The antipsychotic drugs produce an improvement in the mood and behavior of psychotic patients without sedation and addiction. The antipsychotic drugs are represented by the phenothiazines, thioxanthenes, and butyrophenones.

The antianxiety drugs are not basically different from sedative-hypnotics. This is due to the reduced tolerance and physical dependence and higher safety margin of these compounds. The antianxiety drugs are represented by the benzodiazepines, meprobamate, and related drugs.

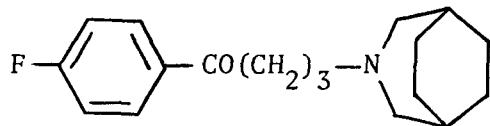
Tranquilizers that employ bicyclic and cage compounds as a part of the active molecule use such compounds as bicyclo[3.2.1]octane, bicyclo[3.2.2]nonane, bicyclo[3.3.1]nonane, and adamantine derived compounds. Some of the bicyclic derived compounds, such as the 3,8-diazabicyclooctane phenothiazine and 2-(4-aryl-1-piperazinyl)bicyclo[3.3.1]nonan-9-ones derivatives act as antipsychotic tranquilizer agents.

Derivatives of phenothiazine, an antipsychotic drug, have been prepared. These compounds are active tranquilizers with low toxicity, long duration of effect, and few side effects.^{28a,b} These compounds have the general formula



and are prepared from 2-trifluormethyl-10-(3-chloropropyl)phenothiazine and 3-hydroxyethyl-3,8-diazabicyclo[3.2.1]octane.

CIBA, Ltd. has prepared 3-[4-(4-fluorophenyl)-4-oxo-1-buty1]-3-azabicyclo[3.2.2]nonane as a tranquilizer.²⁸²



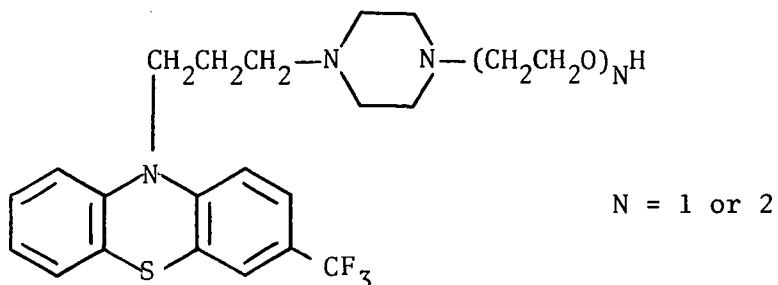
This compound is obtained by heating 3-azabicyclo[3.2.2]nonane and p-FC₆H₄CO(CH₂)₃Cl in the presence of a base or by the reaction of 3-(3-cyanopropyl)-3-azabicyclo[3.2.2]nonane with p-FC₆H₄MgBr.

Grogan has reported the preparation of numerous azabicycloalkanes that have potentially tranquilizing ability.²⁸³ These compounds and their nontoxic addition and quaternary salts are prepared and physical constants given.

Ward²⁸⁴ has prepared 6,7-benzo-2-(4-phenyl-1-piperazinyl)bicyclo[3.3.1]nonan-9-one derivatives. The isomeric axial and equatorial compounds are reported to be novel compounds with tranquilizing activity.²⁸⁵ A series of these compounds was synthesized and some were converted to the 9-phenyl-9-hydroxy derivatives. An activity similar to chlordiazepoxide was demonstrated by 2-(4-phenyl-1-piperazinyl)-9-phenylbicyclo[3.3.1]nonan-9-ol.²⁸⁶

Adamantane carboxyclic acid esters of phenothiazine have found applications as tranquilizers.²⁸⁷ These adamantane carboxyclic acid ester compounds are useful as long acting tranquilizing agents and

are prepared by treating a phenothiazine derivative with an adamantyl



acyl chloride.

Miscellaneous Medicinal Compounds

There are numerous bicyclic and cage compounds that show differential medicinal uses. This section of Chapter 6 is devoted to compounds that have more than three individual medicinal applications. The compounds are arranged according to activity (or function, use) and may be found in Table I listed in alphabetical order according to the specification. The actual compounds listed in column two and other specific uses may be found in column three.

<u>ACTIVITY</u>	<u>BICYCLIC COMPOUND OR FUNCTIONAL GROUP</u>	<u>OTHER USES</u>	<u>REFERENCES</u>
1. amphetamine-like	adamantoylamphetamines		288
2. analeptic	bicyclo[2.2.2]octanes		289
3. antagonists	adamantane-HCl		290
4. veterinary anthel- mintics	1,3-ethanopiperazine		291
5. atherosclerosis	adamantane-HCl		292
6. arteriosclerosis	adamantylamines		293
7. atherogenesis	isostearic adamantylamines		294
8. arrhythmia	1-adamantylamines		295
9. antibacterial	3-azabicyclo[3.2.2]nonane- dithiocarboxyclic acid		296
10. anticataleptic	amantadine hydrochloride		297
11. anticholinergic	8-methyl-3,8-diazabicyclo[3.2.1]- octanes		298
12. antitrichomonadal	3-azabicyclo[3.2.2]nonan-3- ylethoxy		299
13. anticonvulsive	2-ethynlbicyclo[2.2.1]heptan- 2-ols, bicyclo[2.2.1]-5-hept- ene-2-endocarbonyl ureas	hypnotics, sedatives	300a,b

14.	antifibrillation	2, -adamantane acetanilides, adamantylalkylaminoalkylbenz- amides	301a,b
15.	antifilarial	8-methyl-3,8-diazabicyclo- [3.2.1]octane, 2-methyl-2,5- diazabicyclo[2.2.2]octane	302
16.	antihistamines	N-propyl-8-aza-3-bicyclo- [3.2.1]octylbenzhydryl ether	
17.	antiinflammatory	antiemetic, antiallergenic, tranquilizers, hypotensive, depressive, sedative, spas- molytic, analgesic, anti- parasitic, antibiotic	303a,b
18.	antimalarials	N-(dialkylaminoalkyl)adamantane carboximides	
19.	antioxidants	2-hydroxy-3-[w-(1-adamantyl)- alkyl]-1A-naphthoquinones	
20.	antiphysostig- mine	adamantamines	
21a,b,c,d	antitussive	6,6 ⁹ -trialkyl-9-azabicyclo- [3.3.1]nonan-3 -ol esters	
		therapeutic agents, hypo- tensives, antiviral	304
		antitremorine, cholinolytic	305
			306
			307
		9-azabicyclo[3.3.1]nonanes, N-(amino-3,5-dihalobenzyl)- 3-azabicyclo[3.2.1]octanes, 1,2-diazabicyclo[2.2.2]- octanes	308 a,b c,d

22. cardiac stimulants	9-azabicyclo[4.2.1]nonan-2,4-dienes	paroxysmal cardiac dyspnea	309
23. cardiovascular and renal effects	bicyclo[2.2.1]-5-heptene-2-carboxycyclic acid	inhibition of central nervous system	310
24a,b,c choleretic	adamantanes		311a,b,c
25. convulsant	1,3-diazadamant-6-ol		312a,b
26. disinfectants	adamantanes	antivirus agents, dehydrating agents, antioxidants, lubricating additives	313
27. diuretics	3-allyl-3-azabicyclononanes, 3,8-diazabicyclo[3.2.1]octanes, bicycloheptane-, bicyclo-octane-2-2-carboxycyclic acid	pseudocholinesterase inhibiting, antibacterial, cholesterol lowering, hypotensives, antihistaminic, tranquilizing, ganglionic blocking, nervous inhibition, parasites	314a,b,c
28. eurythmic	N-substituted azabicycloalkanes	antiinflammatory, antiatherogenic, antibacterial	315
29. exitant	bicyclo[2.2.1]heptanes	neurotropic, sedative, spasmolytic, anesthetic	316

30.	germicides	bicycloalkylthiphines	medicinals, insecticides	317
31.	glucagon synthesis	1-adamantyloxycarbonyl, N', Nim-bis(adamantyloxy carbonyl)-L-histidine		318a,b
32.	immunosuppressive	adamantoyl cytarabine		319a,b,c
33.	local anesthetic	adamantanes, N-3-azabicyclo-[3.2.2]nonanes	antiarrhythmic, -androgenic blockade, spasmolytic, anti-convulsants, analgesic sedatives.	
34.	miocardia	3,7-diazabicyclo[3.3.1]nonanes		320a,b
35.	mydriatics	8-azabicyclo[3.2.1]octanes		321
36.	mothproofing	2-azabicyclo[3.2.2]nona-6,8-diene-8,9-dicarboxylates	antidepressants, catalysts	322
37.	neuromuscular blocking	bis- -trialkylammonium ethylbicyclo[2.2.1]hept-2-ene, bicyclo[2.2.1]heptane, bicyclo[2.2.2]oct-2-ene		323
38.	neurotropic	3,8-diazabicyclo[3.2.1]octyl derivatives	psychotropics	324
39.	nitrogen retaining	19-nortestosterone-17-(4'-methoxy)bicyclo[2.2.2]oct-2'-ene-1'-carboxylate		325
				326

40.	neuroleptic	3-methyl-3,9-diazabicyclo-[3.3.1]nonanes	327
41.	Parkinsonism treatment	adamantane derivatives	328
42.	prostaglandin synthesis	bicyclo[2.2.1]heptanes	
43.		5'-adamantyladenosine	330
44.	renal function activity	aminoadamantane	331
45.	renin inhibition	adamantyl, adamantylmethyl	332
46.	spinal inhibition	5,7-diphenyl-1,3-diazadamantan-6-ol	
47.	strychnine-like	aryldiazaadamantanones, aryl diazadamantol	333a,b
48.	sedative	various tricyclics	334
49.	sleep-inducing	antihistiminc, antiemetic, antipyretic, hypothermic, local anesthetic, adrenolytic, narcotic effects	335
		5-(2'-aminopropyl)-7-methyl-1,3-diaza-2,4,8-triketobicyclo-[3.2.1]octane, 5-(bicyclo-[3.2.1]octen-2-yl)-5-ethyl-barbituric acid	
		sedative, depressive	336a,b

50. sympatholytic	N- - (1-adamantyloxy)ethyl-cyanamide hydrobromide	hypertonia, viral infections	337
51. sympatheticomimetic	3-carbalkoxy-1-azabicyclo-[2.2.2]oct-2-enes		338a,b
52. synergists	7-oxo-bicyclo[2.2.1]heptane	antagonist, behavior modification	339
53. vasomotor collapse induction	1-aminoadamantane	toxic lesion induction	340
54. weight gain	7-oxo-6,8-dioxabicyclo[3.2.1]-octane		341

CHAPTER 6

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CHAPTER 6

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Chapter 7 - Biochemical Systems Applications

Bicyclic and cage compounds find many applications in studies of a biochemical nature. Such diversified uses as stimulation of insulin release, lipid metabolism effects, sensitization of bacteria, and blocking group preparations are to be found. In this chapter are listed those compounds that have been determined to be biochemically active or useful as a biochemical preparatory compound. The systems that find use as biochemically active compounds include bicyclo[2.2.1]heptanes, bicyclo[2.2.2]octanes, bicyclo[3.3.1]nonanes, and the adamantane derivatives.

Joost, et al¹ have prepared 5- and 6-methyl-2-aminobicyclo[2.2.1]-heptane-2-carboxyclic acids that have been shown to stimulate insulin release as efficiently as leucine and leucine analogues. This study was carried out using the perfused rat pancreas and pancreatic islets.

The interperitoneal administration of exo-2-aminobicyclo[2.2.1]-heptane-2-carboxyclic acid and similar derivatives has been shown to perturb the levels of neutral amino acids in the cerebral cortex while the levels of valine and isoleucine were observed to rise.²

The bicyclic derivative, cantharidin, noted as the principal irritant in Spanish Fly, has been tested, for its effect on incorporation of ³⁵S-labeled sulfate.³ It was found that the uptake of ³⁵SO₂²⁻ was noticeably decreased in di-sodium-cantharidin treated epidermis as compared to trypsin- and untreated tissue.

SC-26096 (2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-6-exo-yl-5(-4-biphenyl)-3-methyl valerate) has been tested on respiration and

oxidative phosphorylation of rat liver mitochondria.⁴ In intact and sonicated mitochondria, NAD-involved respiration was inhibited and succinate-linked respiration was also inhibited but at higher doses. The results of these tests indicates that SC-26096 is bound to mitochondria in vitro.

A rodenticide has been prepared that has an LD₅₀ of 1.8×10^{-1} mg/kg body weight.⁵ This compound, 4-isopropyl-2,6,7-trioxa-1-phosphabicyclo[2.2.2]octane-1-oxide, given interperitoneally to mice produced convulsive seizures and death within minutes. The toxicity of this compound is attributed to the inhibition of acetylcholinesterase in the nervous system,

Agents affecting lipid metabolism have been formulated.⁶ 1,4-disubstituted bicyclo[2.2.2]octane derivatives prepared are studied and spectral properties of these compounds are described.

Bicyclononanes have found pharmacological use in the study of the stereochemistry of microbiological hydroxylation.⁷ Hydroxylation of 3-benzoyl-3-azabicyclo[3.3.1]nonane by Rhizopus arrhizue gives 3-benzoyl-endo-3-azabicyclo[3.3.1]nonan-6-ol and (1R,5R)-3-benzoyl-3-azabicyclo[3.3.1]nonan-1-ol. Chromic acid oxidation studies show that oxidation of 3-benzoyl-3-azabicyclo[3.3.1]nonane gives 3-benzoyl-3-azabicyclo[3.3.1]-nonan-3-one, and N-benzoyl-cis-3-aminomethylcyclohexanecarboxyclic acid. This demonstrates stereoselective microbiological hydroxylation by this bacteria. Other steric phenomenon have been observed with 9-azabicyclo[3.3.1]nonanes.⁸

Mitotic activity of cell cultures has been shown to be decreased by aminoadamantane chloride. This mitotic activity reduction was observed in chick embryo fibroblasts and transplanted HeLa cell cultures. Aminoadamantane is theorized to inhibit the entrance into mitosis by the cell, because direct effect on mitosis once begun was not observed.⁹

An in-vivo technique for assessing the formation of a hemostatic platelet plug has been developed.¹⁰ This technique depends on the formation of a hemostatic platelet plug following puncture in a small vein of the mouse mesentary. Six compounds, among them 5'-adamantyl adenosine were given orally, intravenously, or in the diet and observations on hemostasis observed.

Adamantoyl esters of pyridoxol demonstrating potential usefulness as probes for hydrophobic regions at receptor site of pyridoxal have been formulated.¹¹ These compounds have been prepared in order to investigate the chemical and biological usefulness of adamantyl compounds in vitamin B⁶ chemistry and pharmacology.

Adamantane hydrochloride has been reported to inhibit the mitogenic response of human lymphocytes stimulated with phytohemagglutinin.^{12a} Concentrations of adamantane used to inhibit the response were similar to the concentrations required to inhibit viral replication. The data suggests that adamantane, phytohemagglutinin and lipid containing RNA viruses participate in cell-membrane interactions. This response has also been studied in horses.^{12b}

Adamantanamines and their derivatives have been prepared as sensitizing agents for 5-hydroxytryptamine-induced muscular contraction.¹³ Adamantanes sensitized mucosa-free isolated rat fundus strip with maximal

sensitization observed at approximately 10^{-3} M. Other adamantane derivatives showed less activity and it was concluded that adamantane compounds react with storage sites of 5-hydroxytryptamine or influence the drug-receptor metabolism.

The biological fate of adamantane compounds has been studied. In a report by Geuens and Stephens^{14a} the influence of pH of the urine on the rate of excretion of 1-aminoadamantane was examined. A dose of 150 mg. initially followed by 50 mg/day thereafter at pH 5.0, showed 5 to 7%/hour of the body content excreted. At pH 8.0, this rate was less than 1%. The distribution and excretion of 1-aminoadamantane hydrochloride has been observed by Uchiyama and Shibuya.^{14b} Mice were given orally 1-aminoadamantane hydrochloride and sacrificed 0.25 to 100 hours later. The greatest amount in all organs tested was found in the liver, followed by the kidney, lung, spleen, and heart. Microbiological hydroxylation and demethylation studies in vitro have also been carried out. The bacteria Sporotrichum sulfurescens hydroxylated to N-benzoyl-4 β ,-N-dimethyl-1-adamantylamine to N-benzoyl-4 β ,-N-dimethyl-1-adamantylamine-4,7-diol.^{14c} In rats, the in vivo and in vitro N-demethylation of N,N-dimethyl-3,5,7-trimethyladamantane-1-carboximide, was observed.^{14d} The main route of metabolism was observed to be oxidative demethylation which was enhanced by phenobarbital and inhibited by 2,4-dichloro-6-phenylphenoxyethylamine.

The rat brain has been shown to be a fertile organ of investigation for studies on bioelectric activity and uptake of dopamine and noradrenaline. 1-Aminoadamantane hydrochloride and the sulfate salt analogue activated the bioelectric activity of the cerebral cortex, produced

variations in the rhythm of the hippocampus, and induced a transient bradycardia.^{15a} 1-Aminoadamantane hydrochloride inhibited the uptake of noradrenaline by nerve endings and also inhibited dopamine uptake by 69% at 10^{-3} g/ml concentrations.^{15b}

1-Aminoadamantane has been shown to potentiate the response to L-dopa in mice.¹⁶ These effects include piloerection, salivation, increased motor activity and hyperactivity. Aminoadamantane has also been shown to inhibit DNA synthesis by 24% and decrease the number of cells producing DNA to 30-50%.¹⁷ The average generation time was also increased.

Much of the knowledge of protein structure comes from studies of synthetically produced peptides. In the last few years, the synthesis of large peptide chains showing biological activity has afforded precise correlations between structure and reactivity.

In order to synthesize a peptide it is necessary to protect those groups that are susceptible to reaction but which are required to be free in the final product. This protection is accomplished by blocking groups, and are selected so that they may later be easily removed. A table of suitable blocking groups generally used may be found in the Foundations of Modern Biochemistry series, "Organic Chemistry of Biological Compounds" by Bunker.¹⁸ This table lists the blocking groups that are used for thiol, amine, alcohol, and carboxylate functional groups found in the amino acid structures.

The methods employed for forming peptide bonds involve activation of the carboxyl or amine groups to be joined by reagents that do not

disturb the blocking groups. Earlier methods utilized the acid chloride or azide but newer derivatizing agents are now used.

The cage compounds used in peptide synthesis as blocking groups are virtually all adamantlyloxycarbonyl or adamantyl groups. These groups have been used in arginine, cysteine, histidine, tryptophan, and nucleosides, and have found used in the synthesis of penicillins and cephalosporins.

Jaeger and Geiger¹⁹ have reported that the arginine functional groups can be protected by the adamantlyloxycarbonyl group. Few disadvantages in peptide synthesis is the feature of this method. Approximately 30 peptides are reported to have been synthesized, with good protection of the guanidino function and improved solubility in organic solvents.²⁰ The authors also report use of the adamantlyloxycarbonyl blocking group in cysteine peptide synthesis, useful as intermediates in cysteine-containing peptides.²¹

The adamantlyloxycarbonyl blocking group is prepared from 1-adamantol and dichlorocarbonate. The resulting chloroformate is allowed to react with amino acids to give the 1-adamantlyloxycarbonyl derivatives.²² Some of these derivatives have been obtained in the crystalline state, whereas the corresponding tertbutyloxycarbonyl derivatives have not been reported or are amorphous solids. The adamantlyloxycarbonyl groups are removed by acid-catalyzed solvolysis with trifluoroacetic acid to give the free amino acids.

Other derivatives that have been prepared are the 1-(adamantlyloxycarbonyl)-N-(benzyloxycarbonyl)-histidine and - tryptophan compounds²³

and those that are useful in the synthesis of penicillins and cephalosporin²⁴ and nucleosides.²⁵

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CHAPTER 7

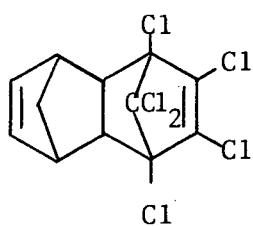
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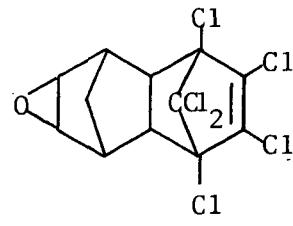
Chapter 8 - Pesticides

For the purpose of this chapter, pesticides will be defined as chemicals that are used to kill insects, fungi, weeds and other pests. Thus, the term pesticide includes insecticides, fungicides, herbicides and similar materials. Insect repellents are also included in this chapter because they constitute a significant group of compounds, but not a large enough group to justify a separate chapter.

Bicyclic and cage compounds have been used extensively as pesticides, and several compounds have received extensive commercial production. Aldrin and Dieldrin are particularly well known insecticides.



Aldrin



Diieldrin

The highly chlorinated compounds such as these have proven to be especially effective. Unfortunately, the long lifetime and other long range physiological effects of these materials that are just now becoming apparent are leading to increased regulations against their use. This trend can be expected to continue, and non-chlorinated alternatives may need to be found.

A difficulty encountered with the literature search in this area is that many of the papers discuss field testing of various materials, and only trade names or codes are given. In those cases, it was difficult to determine what, if any, bicyclic or cage compounds were

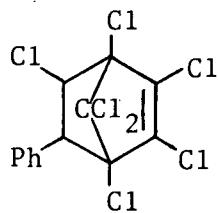
involved. Whenever possible, tradenames were matched to compound structures. Nevertheless, there can be no assurance that the entire literature has been covered in this area.

Fungicides

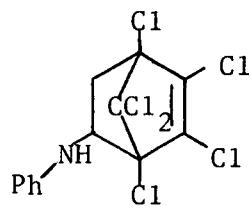
Chlorinated hydrocarbons dominate the bicyclic fungicides.

Bicyclo[2.2.1]heptanes

1,2,3,4,6,7,7-Heptachloro-5-phenylbicyclo[2.2.1]-2-heptene has

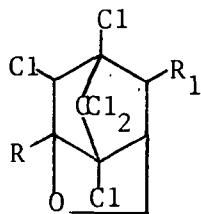


been prepared as a fungicidal material.¹ A similar compound is 1,2,3,4,7,7-hexachloro-5-(aminophenyl)bicyclo[2.2.1]-2-heptene.²



Chlorinated mercury compounds have also been prepared. In particular, N-[alkyl mercuric]-1,4,5,6,7,7-hexachlorobicyclo[2.2.1]hept-5-ene-2,3-dicarboximides and related cycloalkyl, alkenyl, aryl, and aralkyl compounds have been used.³

Compound (8-1) has been found to be effective as a fungicide

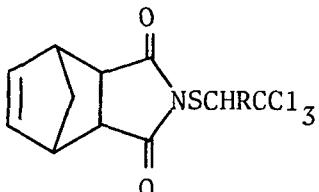


(8-1)

against Alternaria solani.⁴ It also has bacteriostatic (against Staphylococcus aureus), herbicidal, miticidal, insecticidal, and plant growth regulatory activity.

The Propargyl ester of bicyclo[2.2.1]hept-5-ene-2-carboxylic acid and its saturated equivalent has been reported to be useful as a bactericide or fungicide.⁵

Two sulfur compounds have also been reported. Compound (8-2)

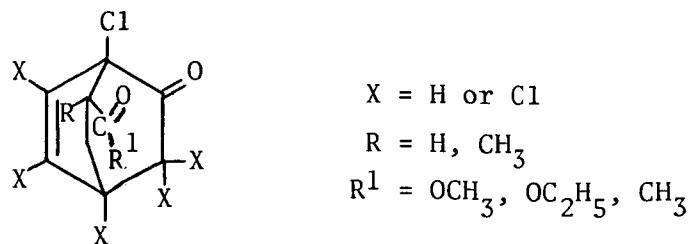


(8-2)

is the only bicyclic compound among several related compounds that was tested against a variety of fungi.⁶ Specific test results are reported. Similarly, 3-(p-tolylsulfonyl)5-chloronortricyclene is reported to be a pesticide and an intermediate for the production of α , β -unsaturated sulfones which are useful as fungicides, bactericides, monomers, and dyestuff intermediates.⁷

Bicyclo[2.2.2]octane

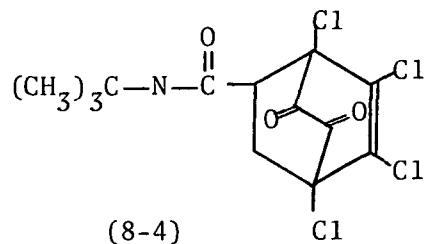
Sims⁸ has prepared several bicyclooctanes similar to (8-3).



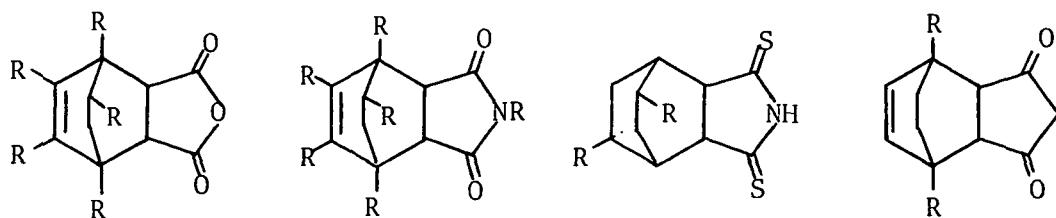
(8-3)

The compounds are fungicides and have been tested against Stemphylium sarcinaeforme and Monilinia fructicola.

Compound (8-4) has been found to be both an effective fungicide

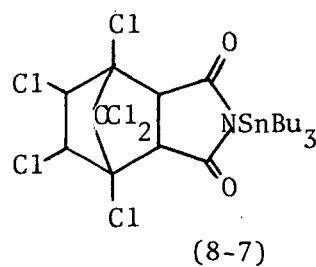
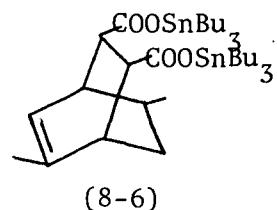
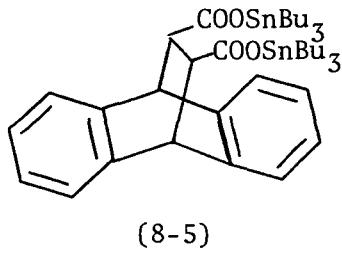


and a useful insecticide.⁹ Derivatives of bicyclo[2.2.1]oct-5-ene



are active against fungi in cereal crops, tobacco, tomato, pumpkin and apple plants.¹⁰ Some of these compounds have shown activity as herbicides and against mites.

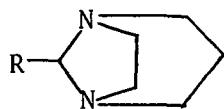
Tributyl tin salts of two bicyclic carboxylic acids (8-5) and (8-6) were tested as fungicides in paints.¹¹ The bicyclic compounds showed generally lower activity than other tin compounds tested. On the other hand, compound (8-7) has been reported to be an effective



fungicide for paints.¹²

Other ring systems

1,5-Diazabicyclo[3.2.1]octanes are useful as fly repellants



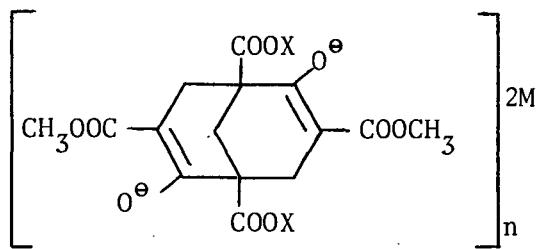
R = C₁-C₈ alkyl, C₆-C₁₂ aryl

preemergence herbicides, and soil fumigants.¹³ When R is H, the soil fungus Rhizoctonia solani was inhibited to the extent of 80% by an application of 75 pounds per acre. Bactericidal and fungicidal activity was also observed with 2,3,4,4-tetrahalobicyclo[3.2.1]octa-2,6-dienes

and 2,3,4,4-tetrahalo-8-oxabicyclo[3.2.1]octa-2,6-dienes.¹⁴



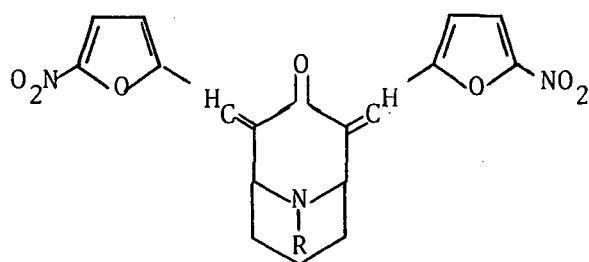
Metal chelates of bicyclononadiene have been used as algicides, fungicides, and bactericides.¹⁵ The specific compound is (8-8).



X = C₁-C₄ alkyl (8-8)

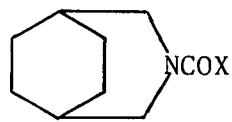
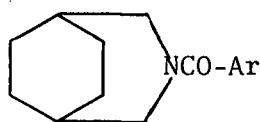
M = Fe²⁺, Fe³⁺, Cu²⁺, Nr²⁺, Al³⁺, Mn²⁺, Cr³⁺, Cl²⁺, Zn²⁺, Br⁻, Pb²⁺, Sn²⁺, Co²⁺, Hg²⁺, ZnO²⁺

Another bicyclo[3.3.1]nonane system that has been used as a fungicide is (8-9).¹⁶

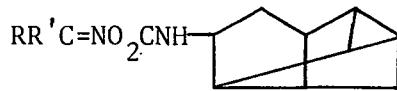


(8-9)

Two 3-azabicyclo[3.2.2]nonane systems have been proposed as fungicides, disinfectants, pigments, dyes, bactericides, central nervous system stimulants, enzyme inhibitors, sedatives and diuretics. Both N-substituted benzoyl derivatives,¹⁷ and carbamoyl derivatives¹⁸ have been prepared.



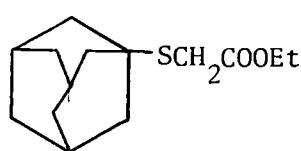
Compound (8-10) has been used for agricultural fungicides.¹⁹



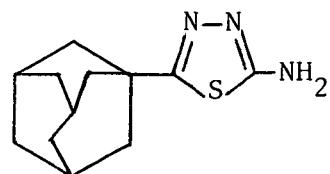
(8-10)

When R, R' was $(\text{CH}_2)_6$, compound (8-9) was formulated into a seed disinfectant.

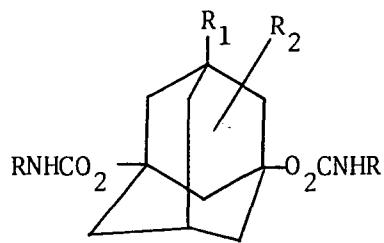
Three adamantane systems that have been suggested as fungicides are (8-11),²⁰ (8-12),²¹ and (8-13).²²



(8-11)



(8-12)

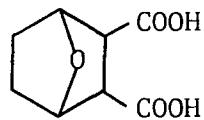


(8-13)

Compound (8-12) was also proposed as a pharmaceutical. Compound (8-13) was particularly useful against Fusarium solani, a soil fungicide that causes root system damage.

Herbicides

The most extensively used bicyclic herbicide is 7-oxabicyclo[2.2.]heptane-2,3-dicarboxylic acid (8-14)



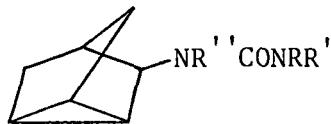
(8-14)

Endothal

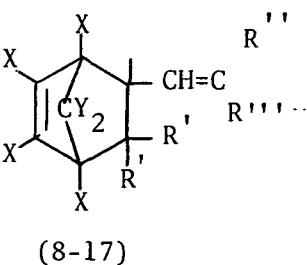
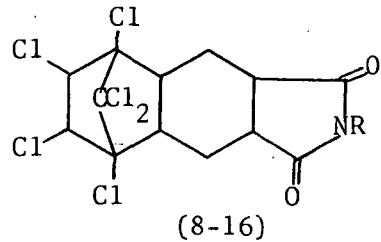
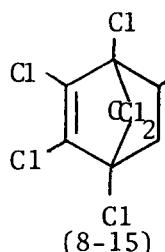
and its sodium salts. This compound has been used extensively. It has also been used as both a preemergence and postemergence weed killer for farm crops. It has also been used as a defolient for potatoes and other crops and to control aquatic plants. It has been commercialized under the name Endothal. The disodium salt is called Aquathal. A suspension of (8-14) and isopropyl-N-phenylcarbamate is known as Murbetal. There are literally hundreds of papers in which (8-14)

under one or more of its trade names has been compared to other herbicides for various crops. Physiological effects and toxicity studies are also common. No attempt has been made to collect the literature in this area.

Bicyclic groups have been used with tributyl tin compounds to produce both pre- and postemergence herbicidal activity.²³ Specifically, the bicyclo[2.2.1]hept-2-yl and 3-nortricyclenyl groups have been used. Preemergence herbicides have also been reported from nortricyclylureas.²⁹



Herbicides derived from hexachlorocyclopentadiene include (8-15), (8-16), and (8-17).



X = Cl, Br

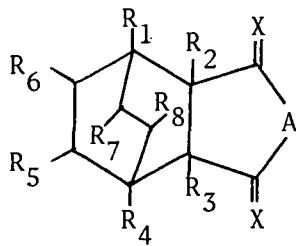
Y = H, Cl, Br, OCH₃

R' = H, lower alky

R'' or R''' = acyl, carboxyl, carbalkoxy, carbometalloxy, cyano, carbamyl

Compound (8-15) afforded complete control of the grass weed Sitaria italicica.²⁵ Compound (8-16) showed almost complete herbicidal effects when R = SnBu₃. It was also effective against a variety of insects.²⁶ Compound (8-17) was suggested as a plant defolient for peaches, cotton, ramie, vine berries, and other field crops.²⁷ It was also suggested for use in regulating the setting of fruit, as a phytotoxic or herbicidal agent, and in the compounding of lubricating oils and rubbers.

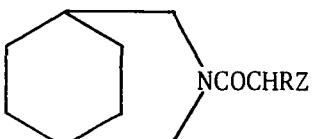
Compounds of the type (8-18) have been prepared and extensively tested for herbicidal activity.²⁸



(8-18)

N-substituted azabicyclooctanes with herbicidal activity have been prepared by Sturm and Vogel.²⁹ Twenty-seven compounds of this type were proposed.

Several N-substituted-3-azabicyclo[3.2.2]nonanes have been reported to be herbicides. For example, N-halomethylcarbonyl-3-azabicyclo[3.2.2]-nonanes have been found to be harmless to cotton and corn while completely inhibiting foxtail grass, barnyard grass, and wild grass.³⁰ Pythium ultimum and Rhizoctonia solani were completely inhibited at a concentration of 30 ppm. Compounds of the type (8-19) have been screened



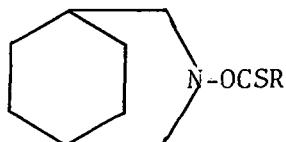
(8-19)

R = H, lower alkyl

Z = halogen, trihaloacetoxy, SCN, or methyl sulfonyloxy

for pre- and postemergence herbicidal activity.³¹ Crabgrass, watergrass, red oats, mustard, and curled dock were controlled by some of these compounds.

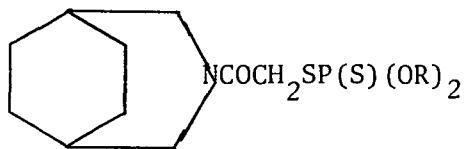
Azabicyclonanonanecarbothiolates (8-20) have been prepared.³²



(8-20)

When R was isopropyl, the compound controlled barnyard grass at two pounds per acre. The allyl compound controlled Johnson grass at 0.5 pounds per acre. Other derivatives showed similar behavior.

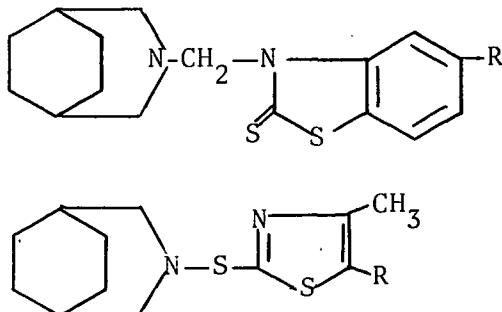
Derivatives of (8-21) were tested as preemergence herbicides



(8-21)

and found to be effective against the seeds of crab grass, annual

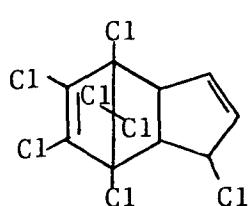
bluegrass, watergrass, red oats, pigweed, and mustard.³³ A variety of weeds and grasses are also killed by 2-mercaptopbenzthiazole and 2-mercaptopthyozol derivatives of 3-azabicyclononane.³⁴



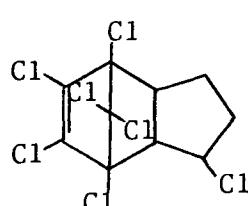
N-Tricyclo[5.2.1.0^{2,6}]decylamide derivatives have been used in the form of solutions, suspensions, and powders as herbicides.

Insecticides

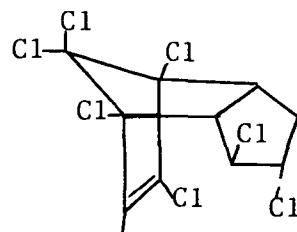
Bicyclic and cage compounds have been used extensively in insecticides. Chlorinated compounds have been used most commonly, and their chemistry has been thoroughly studied. The subject of chlorinated insecticides was reviewed³⁶ in 1974, and will not be covered in detail here. Some of the more common chlorinated bicyclic insecticides are shown.



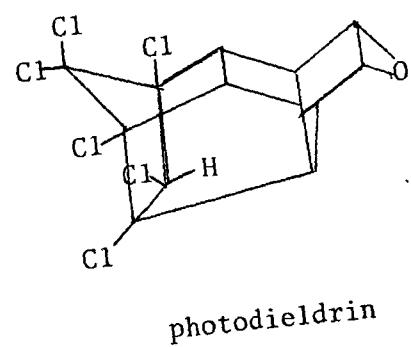
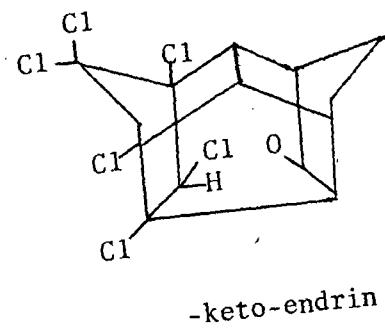
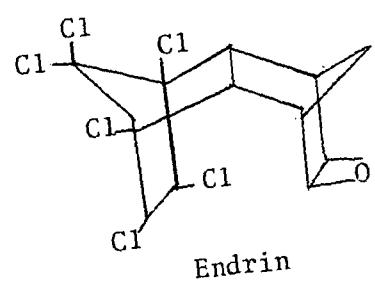
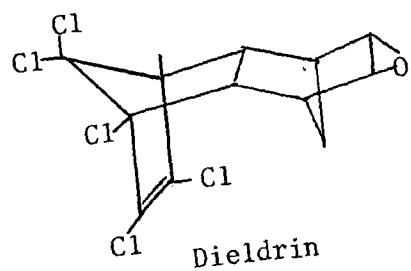
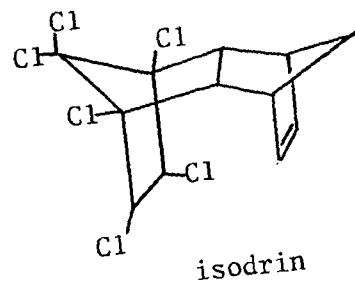
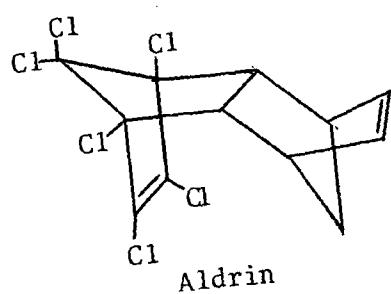
heptachlor

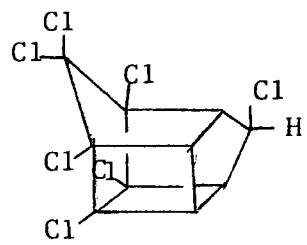


α -DHC

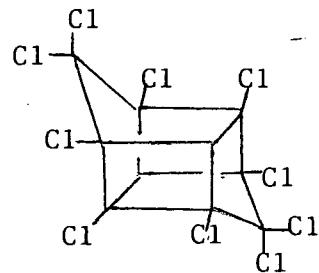


α -chlordane

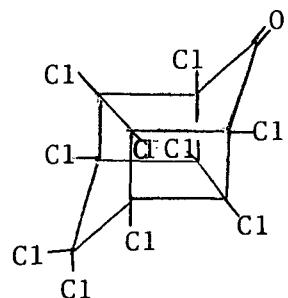




photoheptachlor



Mirex



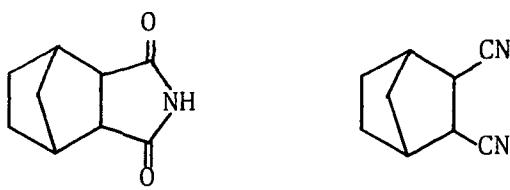
Kepone

In recent years, discoveries concerning long term toxic effects, lack of biodegradability, and other problems associated with the use of chlorinated insecticides have led to increasing restrictions on their use. This situation can be expected to continue. Consequently, the use of chlorinated insecticides will probably decrease as alternate materials are found. In the discussion that follows, the highly chlorinated insecticides have generally been omitted.

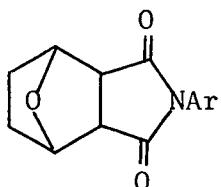
In addition to insecticidal properties of their own, several bicyclic compounds have been used as synergists with other materials, primarily pyrethrins. For example, N-(2-ethylhexyl)-bicyclo[2.2.1]hept-5-ene-2,3-dicarboximide has been found to be especially useful with pyrethrins.³⁷ N-Octylbicycloheptane dicarboximide³⁸ and 1,2-methylene-dioxy-4[2-octylsulfonyl propyl]benzene³⁹ have also proven to be effective. Piperonyl fencholate and α -allylpiperonyl fencholate have been found to have a synergistic effect with allethrin.⁴⁰

N-(2-ethylhexyl)bicyclo[2.2.1]hept-5-ene-2,3-dicarboximide has been found to be an effective insecticide.⁴¹ The N-butyl and N-amyl derivatives have also been shown to have insecticidal activity.⁴²

Koch⁴³ has prepared Diels-Alder adducts of cyclopentadiene and cyclohexadiene with fumaric acid. The products are useful as insecticides, insect repellents, and plasticizers. Dimethyl bicyclo[2.2.1]-hept-5-ene-2,3-dicarboxylate has also been tested and found to be an effective insecticide that works synergistically with other insecticides and insect repellents.⁴⁴ The methyl ester has also been utilized,^{45a} as has the 2-ethylhexyl esters.^{45b} The following related compounds have also been studied:⁴⁶

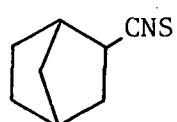


A similar furan derivative is:

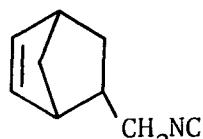


which is useful as a vermicide, and for control of mites, insects, bacteria, fungi, and protozoa.⁴⁷

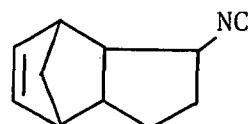
The addition of functional groups to norbornene has also led to insecticidal materials. For example, (8-22),⁴⁸ (8-23),⁴⁹ (8-24),⁴⁹ (8-25),⁵⁰ (8-26),⁵¹ (8-27),⁵¹ (8-28),⁵² (8-29),⁵³ and (8-30)⁵⁴ are either insecticides or insecticide precursors. Some of these compounds also have possible application as plastics and lubricant additives.



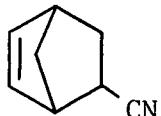
(8-22)



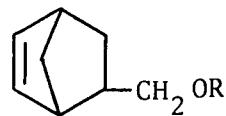
(8-23)



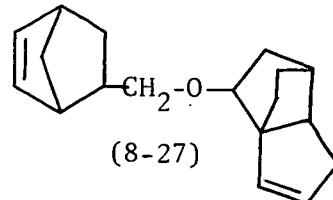
(8-24)



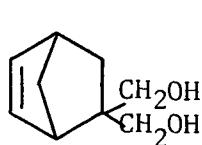
(8-25)



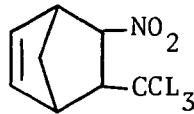
(8-26)



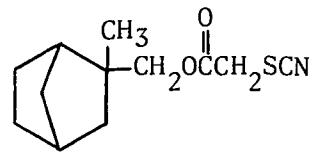
(8-27)



(8-28)



(8-29)

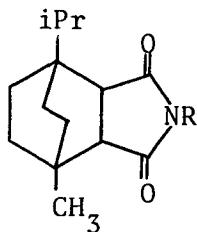


(8-30)

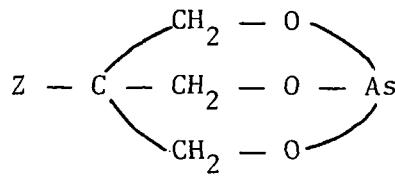
Of a series of terpene oxides that were tested against flies and mealy bugs, menthofuran worked best.⁵⁵ The effect was markedly reduced with bark-beetles.

Neutral 5-bicyclo[2.2.1]-2,3-diazaheptyl esters such as 0,0-dimethyl-5-(N,N-dicarbethoxybicyclo[2.2.1]-2,3-diazahept-5-yl)dithiophosphate have been found useful as insecticides, fungicides, plasticizers, flotation agents, and oil additives.⁵⁶

Carboxylic acid and imide derivatives of bicyclo[2.2.2]octanes have been found useful as insecticides. Thus, N-(octylthiopropyl)-1-isopropyl-4-methylbicyclo[2.2.2]oct-5-ene-2,3-dicarboximide and similar compounds have been reported by Nakanishi, Mukai and Saheki.⁵⁷



Compounds of the type (8-31) have been suggested as insecticidal compositions.⁵⁸

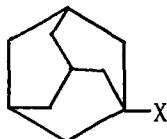


Z = alkyl, aryl, aralkyl,
 alkaryl, cycloalkyl;
 alkoxy, aryloxy, acyloxy,
 acyloxymethyl, benzoxy-
 methyl, chrysanthemumoxy-
 methyl

(8-31)

Aminoadamantane was found to be not highly effective as a chemo-sterilant against house flies, screw worm flies, and boll weevils.

Reduced egg hatch was observed, however, when (8-32) was fed to screw worm flies.⁵⁹



X = CON_3 , $\text{NHCON}(\text{CA}_3)_2$

(8-32)

A variety of 9-thiobicyclononane derivatives have been reported to be useful as insecticides, herbicides, fungicides, bactericides, and nematocides.⁶⁰

Insect Repellents and Attractants

While insect repellents and attractants are not necessarily pesticides in themselves, they are sometimes incorporated into insecticide compositions. Some of the compounds that have been tested for insect repellent activity have also been used in insecticide studies. For these reasons, insect repellents have been included after the insecticide section of this report.

In the 1950's, a series of insect repellent studies were conducted on a wide variety of materials, some of which were bicyclic.⁶¹

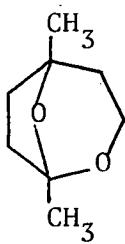
In these and other studies, several thousand materials were screened as potential mosquito repellents. In one paper alone, 4300 compounds were screened.^{61e} As part of the studies conducted during this time, dimethyl bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate was found to be effective against mixed populations of several species of Aedes mosquitoes.⁶²

More recently, Johnson, et al⁶³ evaluated a series of alicyclic, bicyclic, and unsaturated acetals, aminoacetals, and carboxamide acetals. They concluded that compounds with a boiling point of 100-150°/0.5 mm had the optimum degree of volatility. The compounds tested, which included several compounds containing bicyclo[2.2.1]heptane groups, did not appear to have properties as good as N,N-diethyl-m-toluamide. This same compound has also been tested against ticks and mites⁶⁴ and against fleas.⁶⁵

Bicyclo[2.2.1]heptane-2,3-dicarboxylic acid esters prepared from glycols have been used as insect repellents.⁶⁶ Another compound that showed promise was 2-amino-3-isobornyloxy-2-methyl-1-propanol.⁶⁷

Physical properties⁶⁸ and toxicological properties⁶⁹ of a variety of insect repellents have been reported. The effect of insect repellents on plastics and paints⁷⁰ has also been investigated, as has their incorporation into cosmetics.⁷¹

Pine bark beetles have been found to be strongly attracted to the pheromone 1,5-dimethyl-6,8-dioxabicyclo[3.2.1]octane.⁷² Many studies



have been carried out on this pheromone and minor variations.

Miscellaneous Pesticides

In addition to the pesticide compounds already discussed, there are many areas where there were not enough literature citations to justify a separate heading. There are also many examples where the compounds are claimed to be pesticides, but no further details are available. These are all collected in this section.

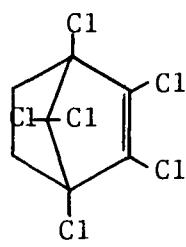
Substituted azabicyclooctanes and nonanes have been suggested for a variety of purposes.⁷³ Fluorosilicates are said to be useful in mothproofing agents. Penicillin salts are useful as aids in purification of penicillins. β -Methyl- α,α -diphenyl- γ -azabicyclooctyl-propanols are useful as acid acceptors in reactions such as dehydrogenation. The thiocyanates, when condensed with formaldehyde, form resinous materials that are useful as pickling inhibitors.

Nematocides have been made from 5-(substituted amino) benzimidazoles.⁷⁴ Among the substituents tested was the 1-adamantyl group. Another nematocide is 1,2,4,7,7-pentachlorotricyclo[2.2.1.0^{2,6}]heptane-3-one-5-sulfonyl chloride.⁷⁵

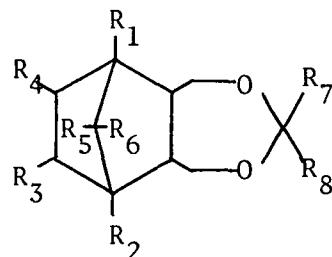
The bis(N,N-dimethylalkylamine) salt of 7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylic acid has been used as a synergist with mercury compounds for the treatment of algae in swimming pools.⁷⁶ The zinc and silver salts have also been used,

Plants treated with disodium-3,6-endohexahydrophthalate are toxic to rodents.⁷⁷ A dye is added to make the plant distinguishable from non-poisonous plants.

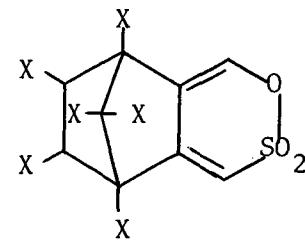
Compounds (8-32),⁷⁸ (8-33),⁷⁹ (8-34),⁸⁰ (8-35),⁸¹ and (8-36)⁸² are all reported to be useful as pesticides, toxicants, and poisons.



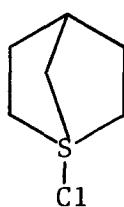
(8-32)



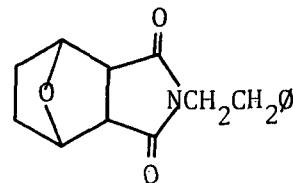
(8-33)



(8-34)



(8-35)

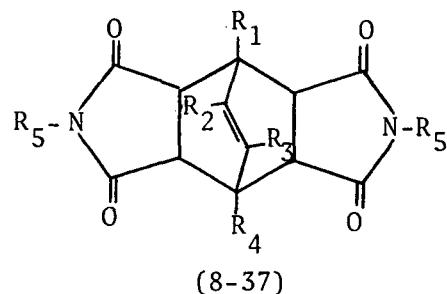


(8-36)

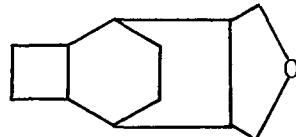
Compounds of the type (8-32) are also reported to be useful as intermediates for pharmaceuticals, plastics, and as fat and oil additives.

Bicyclo[2.2.2]oct-5-ene-2,3-dicarboxylic acid has been proposed as an intermediate for pesticides by Reicheneder and Nebel.⁸³

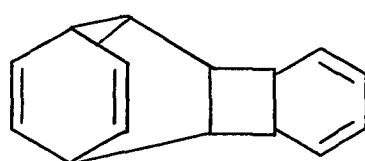
Bluestone⁸⁴ has also found that bicyclo[2.2.2]oct-7-ene tetracarboxylic diimides of the type (8-37) also may be used as pesticides.



Compound (8-38) has been suggested as an intermediate in the formation



of pesticides and pharmaceuticals.⁸⁵ Compound (8-39) has also been



suggested as an intermediate for the formation of agricultural and pharmaceutical preparations.⁸⁶

A number of studies have been conducted to determine the toxicological effect of pesticides on man and warm-blooded animals. Many of these studies have included bicyclic pesticides.⁸⁷ Toxic effects of pesticides on fish have also been studied.

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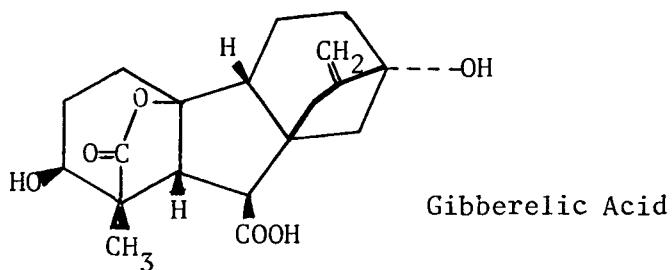
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Chapter 9 - Miscellaneous Applications

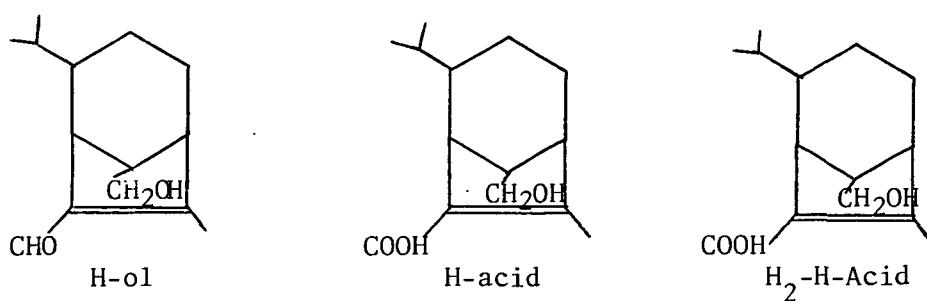
In addition to the applications of bicyclic and cage compounds discussed in the preceding chapter, there are several less extensive areas where these compounds have been used. These areas include plant growth regulators, fuels and fuel additives, lubricants and corrosion inhibitors, and perfumes. Each of these areas could probably benefit from an organized attempt to expand it.

Plant Growth Regulators

The best known plant growth regulators are natural products. The Gibberelins in particular have been well studied over the years,



and are known to significantly accelerate plant growth. Another plant growth regulator that has received considerable attention in recent years is helminthosporol and its derivatives.



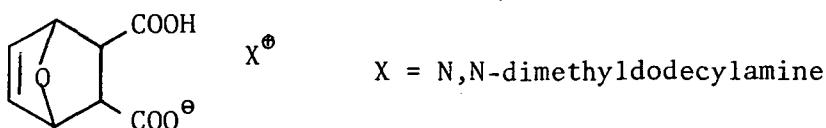
helminthosporol

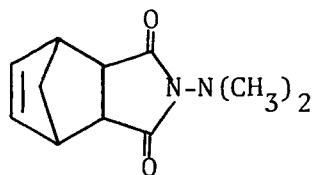
This material was first isolated from the fungus Helminthosporium sativum in 1963 by Tamura, et al.¹

No attempt was made to locate all of the references to naturally occurring growth regulators, and the Gibberelins were specifically eliminated from the search. Some of the key references to the helminthosporol work may be found in the bibliography for this chapter.

The major topic of this chapter is synthetic, bicyclic plant growth regulators. In addition to the compounds discussed here, several of the compounds mentioned in the pesticide chapter, particularly the herbicide section, are also claimed to have plant growth regulatory properties.

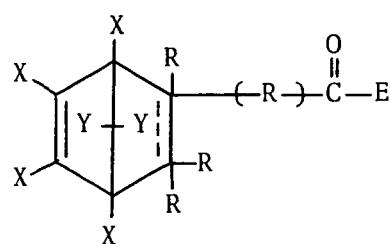
Derivatives of Endothal (7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid) have been found to have plant growth regulatory properties in addition to herbicidal properties.² For example, they have been used to increase the yield of seeds from seed beet plantings³ and to increase the yield of sugar from sugar cane.⁴ Phthalamic acid derivatives of endothal have been used to dwarf⁵ or otherwise affect the growth of plants.⁶ The non-oxygen bridged compound (N-aminobicyclo[2.2.1]hept-5-ene-2,3-dicarboximide) has also been used.^{5,6a} Some of the specific derivatives that have been studied are:





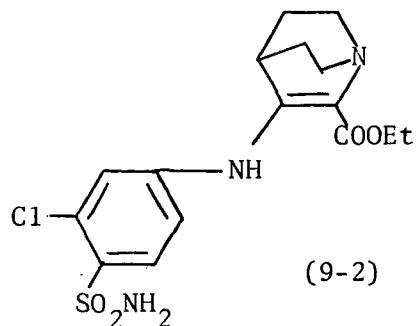
The mechanism of the plant regulatory action is not clear at this time. One possibility is that the derivatives have little or no effect on the plant, but the active ingredient is slowly released by hydrolysis at such a rate that toxic concentrations are not reached. The result of these studies is that a known herbicide and defolient has been modified chemically to produce a series of less active materials. This concept might be worth pursuing further with other pesticidal compositions. In this manner, it might be possible to develop materials that would affect maturing rate, yield, and other characteristics of agricultural crops with a high degree of specificity.

Soloway, Morales, and Overbeek⁷ have found that compounds of the type (9-1) have plant regulatory activity.

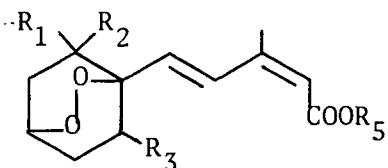


(9-1)

Compound (9-2) is also a plant growth regulator.⁸



Compound (9-3) has been found to completely inhibit germination and



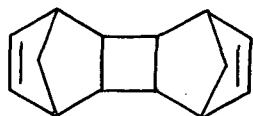
(9-3)

growth of linseed, mustard, ryegrass, and oats when applied pre- and postemergently.⁹ 1,4-Bis(3-hydroxy-2-hexyl)-1,4-diazabicyclo[2.2.2]-octane dihydroxide inhibited the growth of certain microorganisms and plant life.¹⁰ The actions of certain enzymes are also inhibited. The compound was also useful as a polymerization promotor for polyurethane foam.

Fuels and Fuel Additives

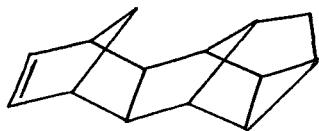
Hydrocarbon fuels usually consist of a mixture of hydrocarbons of optimum boiling range for the particular application. Studies have been conducted with pure hydrocarbons, however, and several bicyclic materials have been found to be useful fuels as a consequence of these studies.

Mixed isomers of pentacyclo[8.2.1.1^{4,7}.0^{2,9}.0^{3,8}]tetradeca-5,11-diene (9-4) have been prepared and tested as energy-rich fuels.¹¹



(9-4)

They have a heat of combustion of about 11 kcal/ml. A similar high energy fuel component is hexacyclo[7.2.1.1^{3,7}.1^{5,13}.0^{2,8}.0^{4,6}]tetradec-10-ene (9-5).¹²



(9-5)

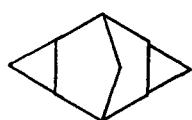
Both of these materials are made by dimerizing bicycloheptadiene.

Thirty-eight compounds, several of which were bicyclic, were tested by Gollis, et al.¹³ Data reported includes decomposition temperature, heat capacity, thermal conductivity, heat of combustion (based on weight and volume), luminometer number, viscosity, freezing point, melting point and hydrogen to carbon ratio. Among the bicyclic compounds tested were pinane and tricyclo[7.1.1.0.0^{4,6}]decane.

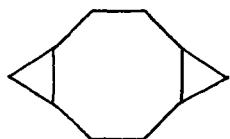
The synthesis of sixty-two hydrocarbons in the motor fuel and lubricating oil range has been reported by Weisser and Trdlicka.¹⁴ Homologs of tricyclo[3.3.1.1]decane were included.

Oxidation of tetracyclo[3.3.1.0^{2,4}.0^{6,8}]nonane (9-6) in a reaction chamber has been suggested as a means of obtaining high thrust.¹⁵

Oxidation of tricyclo[7.1.0.0^{4,6}]decane (9-7) has also been claimed as a source of high thrust.¹⁶



(9-6)



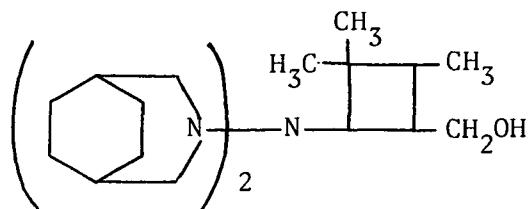
(9-7)

Methyl adamantane and dimethyladamantane have been claimed as jet fuels, or components of jet fuel blends.¹⁷ They are also said to be useful in the preparation of diester type lubricants.

Fuel oils have been stabilized with a polyvalent metal salt of the monoamide of bicyclo[2.2.2]oct-2,3-dicarboxylic acid.¹⁸ Terpenes have been condensed with maleic, fumaric, citraconic, mesaconic, aconitic, and itaconic acids, their anhydrides and esters, to form hydrocarbon stabilizers that are said to prevent sludge formation in fuel oils, cutting oils, and other types of oils.¹⁹

1-Azabicycloalkanes have been found useful in gasoline, fuels and lubricants to stabilize against sludge formation.²⁰

The compounds are also useful as agricultural chemicals.^{20b} Compound (9-8)



(9-8)

was one of a variety of 2-dialkylaminocyclobutane-1-methanols that were said to be useful as fuel oil stabilizers.²¹

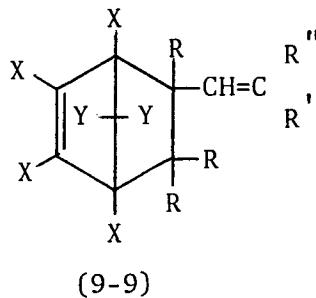
Triethylenediamine and trimethylenediamine have been treated with $((\text{CH}_3)_3\text{N})_3\text{B}$ at 140-200° to form additives for motor fuels.²² The compounds are also said to have anticorrosive properties when incorporated into lubricating oils.

Lubricants and Corrosion Inhibitors

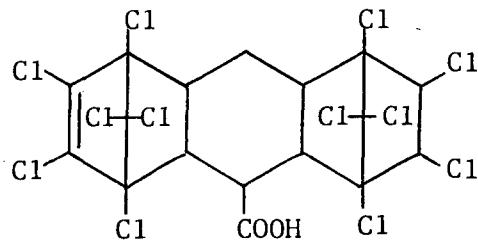
Bicyclic compounds have been incorporated into lubricants as both the main constituent of the oil and as additives. Adamantane groups in particular have been used in some of the diester types of synthetic lubricating oils. Some of the fuel additives discussed in the previous section are also useful as lubricant additives.

Terpenes have been incorporated into lubricant compositions by Brennan and Raybould.²³ They found that a sulfurized phosphorized terpene alcohol would impart antiwear characteristics to a mineral oil. Thompson²⁴ has reported that terpenes may be treated with alpha, beta unsaturated polycarboxylic acids and appropriate N-alkyl-ethanolamines to form a corrosion inhibitor.

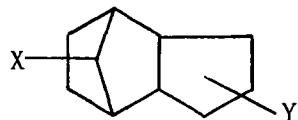
Soloway²⁵ has suggested that compound (9-9) might be useful as a lubricating oil additive.



The condensation products of hexachlorocyclopentadiene with 1,4-dehydrobenzoic acid are also useful as components of lubricants or as insecticides.²⁶



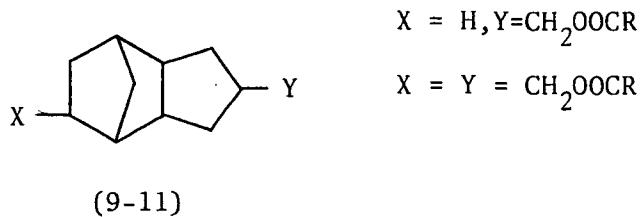
Esters such as (9-10) are said to be excellently suited as softeners



$X = -COOCH_2R, -CH_2OOCR$

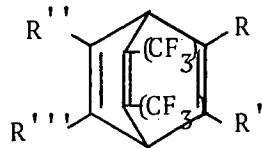
$R = \text{hydrocarbon up to 170 atoms}$

and as high grade lubricating oils.²⁷ The related compound (9-11) has



also been used as a lubricating oil, a softener, and in the lacquer and plastic industry.²⁸ Hydraulic oils and electrotechnical insulation have also been suggested as uses for these compounds.²⁹ Other derivatives of dicyclopentadiene containing chlorine, mercaptane, sulfide, or polysulfide groups are suggested for high pressure lubricant additives.³⁰ A 4% concentration of the additive increased the extreme pressure index of a basic aircraft oil from 10 to 104.

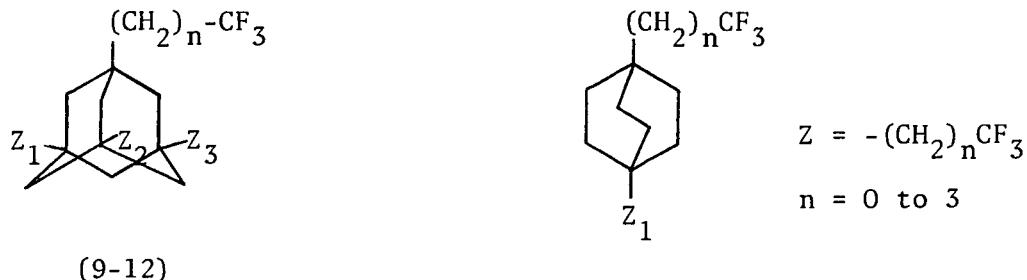
Bis(trifluormethyl)substituted bicyclo-octatrienes have been



suggested as heat transfer and pressure fluids.³¹

Lubricating oils have been improved by adding small amounts of the polyvalent metal salt of the monoamide of a dicarboxylic acid. Alkyl-substituted bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid was one of the acids specified.³² Both detergent³² and antirust³³ properties were mentioned for these compounds.

Compounds of the types (9-12) and (9-13) are useful as heat transfer

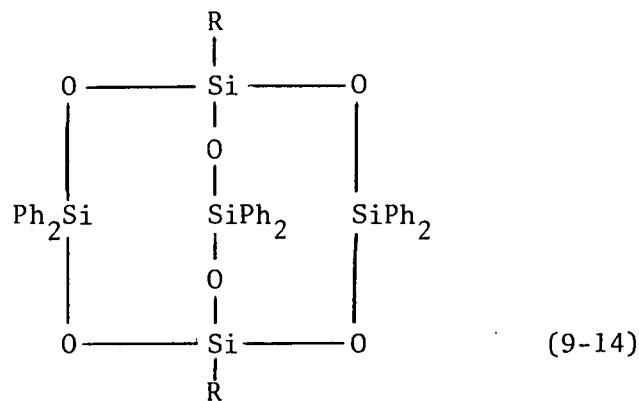


fluids and working fluids in Rankine Cycle engines.³⁴

Ester lubricants, antifreeze, and components of alkyd resins have been made from 1-hydroxymethyl-6,8-dioxabicyclo[3.2.1]octane.³⁵

Another heterocyclic system is 9-chloro-3-oxabicyclo[3.3.1]nonane which is used as a cutting oil to make threads in stainless steel pipe.³⁶

A high or low temperature liquid lubricant or hydraulic fluid is made from compound (9-14) and organopolysiloxanes.³⁷

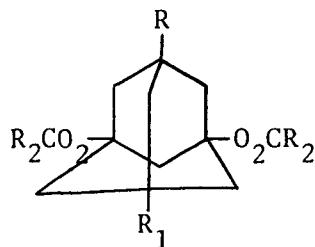


Compound (9-14) can also be ring opened by heating with 0.001-0.1% of an alkaline material to form insulators and heat resistant coatings.

A crystal of adamantane was used in a surface slip test by fastening crystals to a disk base plate.³⁸ It was determined from this study that the average molecule moved about one millimeter before being desorbed.

Methyl and dimethyladamantanes prepared by isomerization of C₁₁₋₁₂ tricyclic napthalenes have been found useful in diester type lubricants, as jet fuels, and as components of jet fuel blends.³⁹ Ethyl substituted adamantanes are reported to have high thermal stability and are useful as cooling agents and lubricants.⁴⁰

Esters of 1-carboxyadamantane had good thermal stability and good stability against radicals but poor oxidation stability in the presence of metals. Poor load carrying capacity was also observed, but this could be improved with a small quantity of oleic acid.⁴¹ Adamantane diesters have also been prepared as lubricants.⁴²

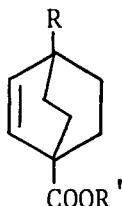


Poly(3,5-dimethyl-1-adamantyl acrylate) has been suggested as a viscosity index improver.⁴³ 1,3-Diaminoadamantane dinitrite has been reported to be a corrosion inhibitor.⁴⁴

Perfumes

Many constituents of perfumes are naturally occurring materials. Terpenes and esters are common. Many of these materials are bicyclic. As a consequence, it is not unreasonable to expect that some synthetic bicyclic compounds also might find use in perfumes.

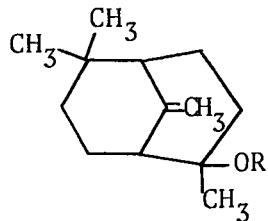
Kretschmar and Erman⁴⁵ have prepared 2-methylene-3-exo(trans-4'-methyl-5'-hydroxypent-3'-enyl)bicyclo[2.2.1]heptane and related compounds for use as perfumes. Bicyclo[2.2.2]octenes of the type (9-15) have also been prepared as perfume intermediates.⁴⁶ Bicyclo[2.2.2]octane-



(9-15)

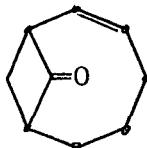
2-carboxaldehyde has been condensed with methyl ethyl ketone to produce a perfume material.⁴⁷

Ethers of 4,8,8-trimethyl-9-methylene[3.3.1]bicyclo-4-nonanol have been reported to have a strong woody amber-like scent that decreases in intensity with increasing atomic weight.⁴⁸



A grassy-weedy camphoraceous order is obtained from compounds related to (9-16).⁴⁹ They have been incorporated into perfume, flavor, and

detergent compositions. Bicyclo[3.3.1]nonanes have been irradiated to form bicyclo[5.1.1]non-2-en-9-one.⁵⁰

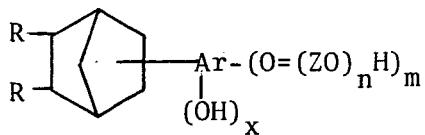


The corresponding bicyclo[4.1.1]octane-8-one has also been reported. These compounds have a fougere odor and have been formulated into detergents.

8-oxatricyclodecane is reported to be useful as a solvent and as a component of perfumes.⁵¹ Perfume compositions have also been made from adamantane derivatives.⁵² For example, 1-adamantyl methyl ketone, ethyl 1-adamantylcarboxylate, and 1-adamantylnitrile have been used.

Detergents

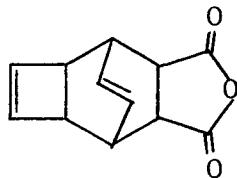
Schmerling has prepared compounds of the type (9-17) which have



(9-17)

surface active properties.⁵³ An alkyl bicycloheptylarylsulfonate containing at least three carbon atoms in the alkyl group has also been claimed as a surface-active agent.⁵⁴ Mono- or dialkylsubstituted

bicycloalkane sulfates, sulfonates, and hydroxy polyoxyalkylenes in which the alkyl substituent contains up to 18 carbon atoms are useful as biodegradable detergents.⁵⁵ Polycyclic decarboximides made from compound (9-18) were found to be stable to ultraviolet light and are

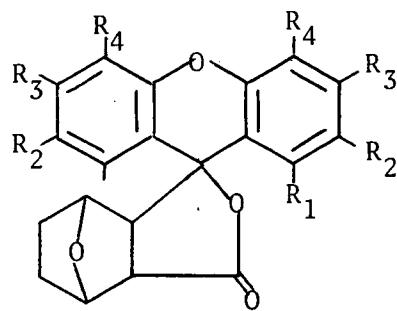


(9-18)

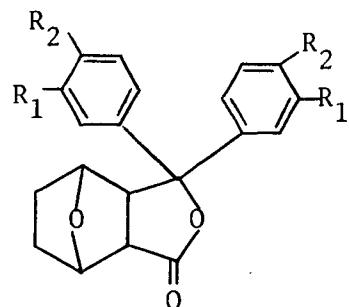
useful as optical brighteners and as light protectors.⁵⁶

Dyes and Dye Intermediates

Fire retardant pigments are reported to be derived from hexachlorocyclopentadiene.⁵⁷ Compounds (9-19) and (9-20) are phthalein dyes.⁵⁸

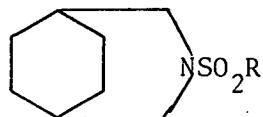


(9-19)



(9-20)

3-Azabicyclo[3.2.2]nonane sulfonamides are purple pigments that are

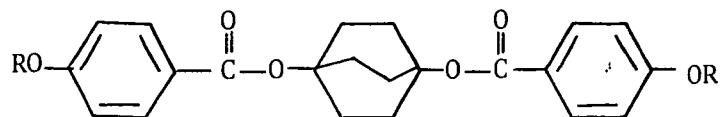
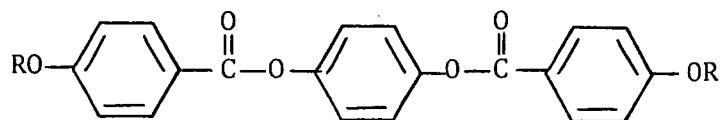


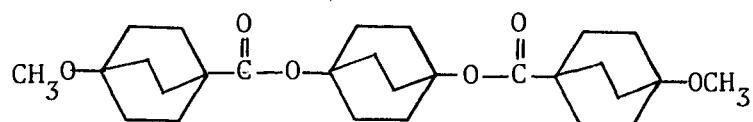
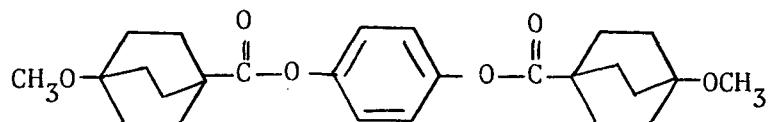
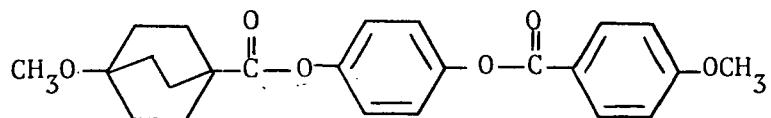
suitable for aqueous dispersion.⁵⁹

The incorporation of bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid into an acrylonitrile-methyl acrylate copolymer gave a polymer that would absorb Blue K and Red 2S cation dyes better than materials that did not contain the bicyclic group.⁶⁰ 3-(p-Olylsulfonyl)-5-chloro-nortricyclene was one of several compounds which are reported to be useful as dyestuff intermediates, pesticides and monomers.⁶¹

Liquid Crystals

Dewar⁶² has studied the effect of replacing benzene rings in liquid crystals with bicyclo[2.2.2]octane groups.





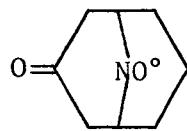
The object of the study was to prepare a liquid crystal material that could be used as a solvent for spectroscopy. Replacement of the central ring by a bicyclooctyl group lowered the transition temperature 28°. Replacement of a terminal group lowered the transition temperature by 76°. No mesophase was observed when both terminal phenyl groups were replaced, but the value was estimated to be 167° from a phase diagram. Thus, the two effects appear to be additive. No liquid crystal behavior could be observed when all three phenyl groups were replaced.

The authors concluded that a linear geometry is the prime factor in generating liquid crystal behavior. The aromatic character of the benzene ring was also found to be important by providing polarity for the ends of the molecule. It was suggested that terminal groups will

be necessary to make an ultraviolet transparent liquid crystal. A suggestion was made that the liquid crystals described here might be suitable as the liquid phase in gas chromatography for the separation of position isomers.

Miscellaneous Applications

A cigarette filter paper impregnated with bicyclo[3.3.1]nonan-3-one-9-oxyl is said to remove 45 to 55% of the nitrosyl radicals from



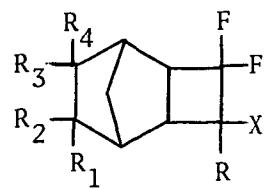
the smoke passing through the filter.⁶³ Tobacco additives have been made from non-volatile, flavor containing Diels-Alder adducts.⁶⁴

Light sensitive photographic recording materials have been made using 4,8-bis(tricyclo[2.2.1,0^{2,6}]heptan-3-ylcarboamoyl)-1,5-naphthalene-dicarboxylic acid as one component.⁶⁵ Poly-p-Xylylenes have been used as a photomasking system with improved resolution and reproductibility.⁶⁶

Natural and synthetic resins containing bicyclic groups have been tested for paper sizes.⁶⁷ Pine resin has been converted to a drying oil for paints and varnishes by fractionation and thermal isomerization.⁶⁸ A study has also been made on foaming properties of pine oil for mineral flotation.⁶⁹

Fire resistant bituminous preparations for roof coverings have been prepared by mixing the bituminous material with perchloropentacyclo-[5.2.1.0^{2,6}.0^{3,9}.0^{5,8}]decane and other polyhalogenated compounds.⁷⁰ A recipe containing these materials with a small amount of antimony oxide and asbestos does not burn.

Degreasing agents for metals and spotting agents for textiles have been made from compounds like (9-21).⁷¹



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CHAPTER 9

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Chapter 10 - Suggestions for Further Work

Suggestions for further work have been made in appropriate places throughout this report. It is the purpose of this final chapter to collect these suggestions together, adding additional suggestions where they might be useful.

Polymers

The use of bicyclic and cage compounds in polymers was discussed in Chapter 5. A few individuals, especially at du Pont, seem to have undertaken a reasonably thorough study of bicyclic monomers. As a consequence of their work, bicyclic equivalents of many of the common bicyclic compounds have been prepared and incorporated into polymers. In general, the resulting polymers have been reported to have improved thermal properties. Unfortunately, no uniform method of testing seems to have been used, and it is difficult to determine which, if any, of the reported materials might have useful commercial properties.

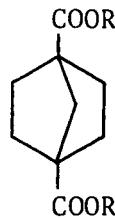
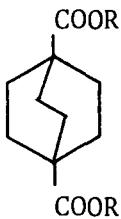
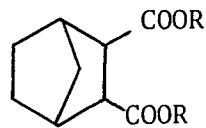
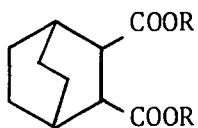
If this area is ever to be developed for commercial purposes, it will be necessary to evaluate each of the polymers using a uniform, standard procedure. Special criteria might be established for special applications, such as paints or potting compounds.

Possible economic restraints on the commercialization of bicyclic polymers were discussed at the end of Chapter 5. If suitable polymers can be identified, it will still be necessary to find economic synthetic routes to these materials. This could be a major problem, except for highly specialized applications.

The use of bicyclic peroxides as polymerization initiators may have some potential. Little work has been done with these compounds, and they do show unusual stability. Unfortunately, a range of peroxides with varying decomposition temperatures is already commercially available, and there may not be much incentive to develop another series of compounds.

A possible method of making a micro-sized capacitor is described in Chapter 5. The idea proposes to take advantage of the ultrathin films that can be made with p-xylylenes. Fluorinated poly-p-xylylene and a thin metal film deposited by a vapor deposition technique might be used to make a small capacitor suitable for use at high temperature.

Unlike monomers and polymers, bicyclic polymer additives have not been studied in an organized manner. As a consequence, this should be an area with potential for further development. Compounds containing bicyclo[2.2.1]heptane and bicyclo[2.2.2]octane groups should be especially useful. Bicyclic equivalents of presently commercial polymer additives in particular might have similar properties to the non-bicyclic compounds and be more stable at high temperatures. Bicyclic equivalents of dibutyl and dinonyl phthalates might be particularly useful.



R = Butyl or Nonyl

Tricresyl phosphate, triphenylphospite, and triphenyl phosphine are three compounds that are presently used in polymers that are designed for high temperatures. Bicyclic equivalents might offer even greater thermal stability without greatly affecting the physical properties of the polymer.

Medicinals

Bicyclic and cage compounds demonstrate a wide variety of medicinal applications as parent drugs or as important drug components. In view of the physiological activities of these compounds and the high potential for unknown effects, one should investigate these systems with caution.

Interesting avenues of research may be found in such areas as analgesics, antibacterials, anticancers and various other topics. For example, one study that could be undertaken would be to study known drugs using bicyclic groups in place of the existing aromatic systems. A study of the changes in physiological effects of these modified compounds may lead to new drug compositions or may even enhance the understanding of drug actions.

The slow hydrolysis of bicyclic esters could be useful in developing timed-release drugs. Salicyclic acid substituted with the bicyclic analogue might give long-lasting relief to arthritis victims. As another example, some bicyclic compounds have been reported to be more potent than meperidine (Demerol). These compounds might best be studied by investigating the toxicological parameters. Similarly, systems that show high analgesic activity with low toxicity or slow release properties might be investigated to determine what other derivatives of the parent compound will show these properties.

Synthesis of penicillin derivatives with activities superior to natural compounds has proved to be a fertile avenue of drug research. Bicyclic or cage penicillin compounds that demonstrate excellent acid sensitivity, resistance to penicillinase, and slow intestinal absorption could be expanded by searching out other three-dimensional, side-chain derivatives with these beneficial properties.

✓ Various arabinofuranosylloytosineadamantoate compounds have demonstrated excellent potency as anticancer agents. Other "sugar" derivatives might be investigated that demonstrate inhibitory actions and are also suitable as depot agents.

Compounds that show increased activity or increased specificity should be exploited. For example, anticholinergics with the 9-azabicyclo-[3.3.1]nonane skeleton show enhanced activity when gem dialkyl groups are introduced into the bicyclic skeleton. These compounds are more active than atropine, scopolamine, and benactyzine, which are known anticholinergics.

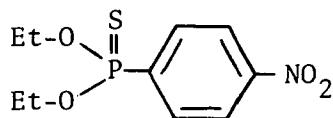
Selected antiinflammatory medicinals such as the quinuclidines are more effective than known compounds but more toxic. An in-depth study concerning the reduction of this toxicity by chemical means should prove to be a valuable project.

Generally, in the other categories considered in this report, there are few outstanding examples of medicinal superiority. A comprehensive study does not seem to have been undertaken, however, and further work might be worthwhile.

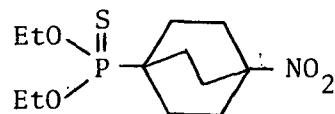
Pesticides

With polychlorinated pesticides in general disfavor at the moment, increased use of non-chlorinated pesticides can be expected. Although it is difficult to visualize which types of compounds will be preferred, bicyclic and cage compounds will undoubtedly find increased use.

One approach to the problem might be to synthesize bicyclic analogs of known pesticides in order to modify the toxicity of the product. Parathion is one example that is highly toxic and which might be affected by a switch to a bicyclic analog.



Parathion



A bicyclic analog

The generally slow rate of hydrolysis of esters of bicyclic and cage compounds suggests another area that might be worthwhile. It should be possible to incorporate slow release characteristics into pesticide composition by making bicyclic esters. This property would make it possible to have an effective pesticide that does not need to be applied as often as present pesticides. Toxicity to humans might be lowered by this technique also.

There is already evidence (see Chapter 8) that low levels of certain herbicides can cause plant dwarfing and other effects. If the effective concentration of the herbicide could be maintained at a relatively low

level by making a bicyclic ester of the herbicide that would hydrolyze slowly, then it might be possible to develop new horticultural techniques for growing dwarf plants for specific purposes.

Synthetic Lubricants

At the present time, there is a rapidly developing trend toward the use of synthetic lubricants. This trend is creating a demand for temperature-resistant materials to form both the bulk of the lubricant and as additives to improve specific characteristics. The unusual thermal stability of many bicyclic and cage compounds suggest that they should have a significant part in this emerging technology.

There is ample evidence (see Chapter 9) that this is true. Several good diester lubricants have been reported that use a bicyclic nucleus as part of the molecule. There are also several reports of bicyclic compounds being used as lubricant additives.

At the same time, the literature in this area is not extensive. No concerted effort seems to have been made to exploit this area. This situation suggests that there is a real opportunity to undertake a concerted attempt to find new bicyclic and cage compositions that might be useful as synthetic lubricants or lubricant additives.